Organic Chemistry II

Organic Chemistry II

XIN LIU

KWANTLEN POLYTECHNIC UNIVERSITY
SURREY

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Contents

Licensing Info ix

Accessibility Statement x

For Students: How to Use This Book xii

Acknowledgements xiv

Chapter 1: Alcohols and Ethers

1.1 Structures, Naming and Physical Properties 3

1.2 Reactions of Alcohols 6

1.3 Synthesis of Alcohol from Alkenes 15

1.4 Synthesis of Alcohols from Carbonyl Compounds 18

1.5 Williamson Ether Synthesis 34

1.6 Practices 36

1.7 Practices Answers 38

Chapter 2: Aldehydes and Ketones

2.1 Structures, Properties and Naming of Aldehydes and Ketones 43

2.2 Preparations of Aldehydes and Ketones 47

2.3 Reactivities of Aldehydes and Ketones 50

2.4 Addition of Water to Aldehydes and Ketones 54

2.5 Addition of Alcohols to Aldehydes and Ketones 56

2.6 Protecting Groups in Synthesis 64

2.7 Addition of Amines and Amine Derivatives to Aldehydes and Ketones 66

2.8 Wittig Reaction 74

2.9 Baeyer-Villager Reaction 80

2.10 Practices 83

2.11 Practices Answers 85

Chapter 3: Conjugated Unsaturated Systems

3.1 Simplest Conjugated System: Allyl System 89

3.2 Reactions of Allyl System 92

3.3 Conjugated Dienes 96

3.4 Reactions of 1,3-Butadiene 100

3.5 Diels-Alder Reaction 104

3.6 Practices 116
3.7 Practices Answers 118

Chapter 4: Aromatic Compounds

4.1 Naming of Benzene and Benzene Derivatives 123
4.2 Reactivity, Stability and Structure of Benzene 125
4.3 Hückel's Rule: Aromatic, Anti-aromatic and Non-aromatic Species 128
4.4 Heterocyclic Aromatic Compounds 133
4.5 Electrophilic Aromatic Substitution (EAS) of Aromatic Compounds 136
4.6 Common EAS Reactions 139
4.7 Friedel–Crafts Reactions 144
4.8 Practices 153
4.9 Practices Answers 155

Chapter 5: More Reactions on Aromatic Compounds

5.1 Activating or Deactivating Effect of the Substituents on EAS 159
5.2 Directing Effects of the Substituents on EAS 163
5.3 EAS on Di- or Tri-substituted Benzenes 172
5.4 Synthesis of Benzene Derivatives 173
5.5 Arenediazonium Salt 179
5.6 Nucleophilic Aromatic Substitution: SNAr 184
5.7 Practices 189
5.8 Practices Answers 191

Chapter 6: Reaction at the α-Carbon of Carbonyl Compounds

6.1 The Acidity of the α-Hydrogens 197
6.2 Halogenation of the α-Carbon 202
6.3 Alkylation at the α-Carbon 206
6.4 Aldol Reactions 209
6.5 Reactions of α,β-unsaturated Aldehydes and Ketones 219
6.6 Practices 228
6.7 Practices Answers 230

Chapter 7: Carboxylic Acid and Derivatives

7.1 Nomenclatures and Physical Properties of Carboxylic Acid Derivatives 235
7.2 Preparation of Carboxylic Acid 241
7.3 Reactions of Carboxylic Acid and Derivatives: Nucleophilic Acyl Substitution 244
7.4 Acyl Chloride and Carboxylic Acid Anhydrides 248

7.5 Esters 252
7.6 Amides 257
7.7 Other Reactions of Carboxylic Acid Derivatives 259
7.8 Reactions of Nitriles 266
7.9 Practices 270
7.10 Practices Answers 272

Chapter 8: The Claisen Condensation and Applications in Synthesis

8.1 Claisen Condensation Fundamentals 277
8.2 Other types of Claisen Condensation 280
8.3 β-dicarbonyl Compounds in Organic Synthesis 284
8.4 Practices 291
8.5 Practices Answers 293

Chapter 9: Carbohydrates

9.1 Classification and Configurations of Carbohydrates and Monosaccharides 297
9.2 The Cyclic Structure of Monosaccharide and Mutarotation 302
9.3 Other Reactions of Monosaccharides 308
9.4 Oxidation and Reduction Reactions of Monosaccharides 310
9.5 Degradation and Synthesis of Monosaccharides 317
9.6 Disaccharide 319
9.7 Practices 323
9.8 Practices Answers 325

Special Topic: Types of Common Organic Reaction Mechanisms and Understanding the Names of Reaction Mechanisms 329
Versioning History 332

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Acknowledgements

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CHAPTER 1: ALCOHOLS AND ETHERS

1.1 Structures, Naming and Physical Properties

1.1.1 Alcohols

Alcohol is a type of compound that contains one or more hydroxyl hydroxy (OH) groups bonded to a saturated carbon atom (or sp^3 hybridized carbon). The most common alcohol in our daily life is ethanol, with the formula of C_2H_5OH, which is the active ingredient in all alcoholic beverages. Fermentation of the sugars from a variety of sources, for example, fruit juices, and grains, with the help of yeast produces ethanol. Methanol, the smallest alcohol, was used to be produced by heating wood at a high temperature in the absence of air, therefore has another name "wood alcohol". As an important industrial chemical today, most methanol is produced by the catalytical hydrogenation of carbon monoxide with high pressure and high temperature.

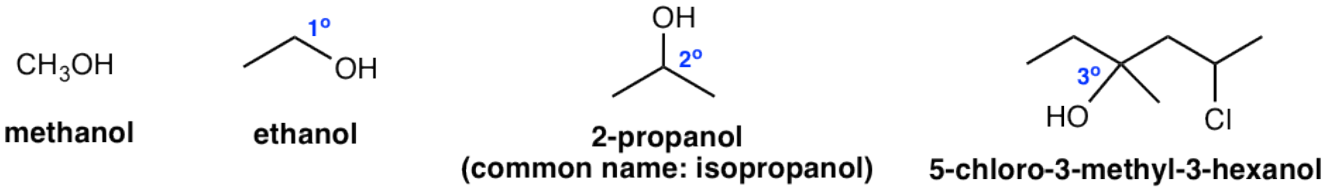


Fig. 1.1a Structure and naming of a few alcohol examples

The nomenclature rules we learned in **section 2.4 in Book I**, cover the IUPAC naming of simple alcohol compounds (as the examples given in Fig. 1.1.a). Alcohols could also be classified as 1° (primary), 2° (secondary), or 3° (tertiary), depending on the number of carbons bonded to the alcohol carbon, as shown in the above examples.

Compounds that have an OH group connected directly to a benzene ring are called phenols. Phenol is a type of aromatic alcohol.

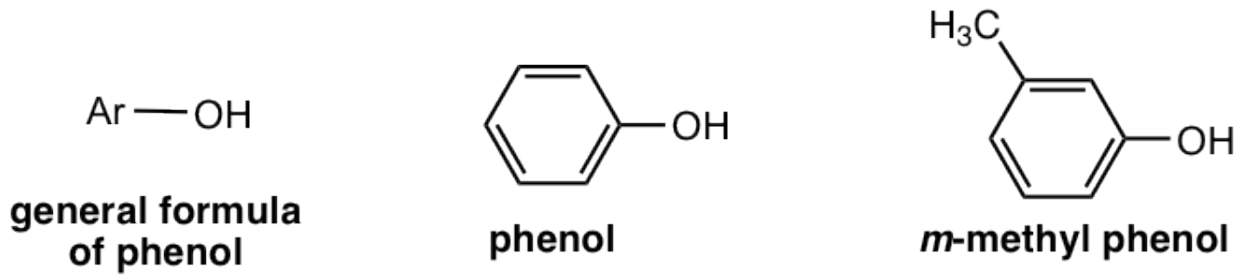


Fig. 1.1b Structure of general phenol, phenol, and substituted phenol

The alcohol group may also be part of a more complex molecule, for example in vanillin and cholesterol. Some larger molecules can contain multiple OH groups, such as in albuterol, the chemical ingredient used in some respiratory medicines for the treatment of difficulty breathing.

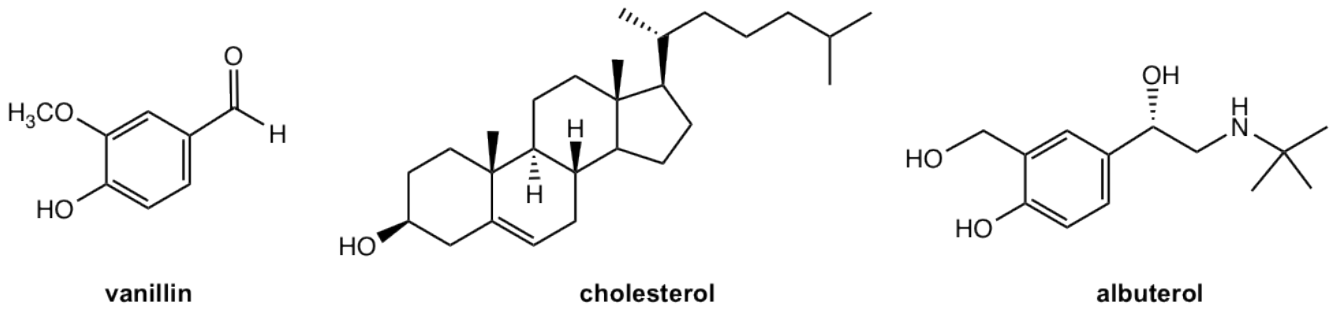


Fig. 1.1c Structure of cholesterol, vanillin and albuterol

The physical properties of alcohols, such as boiling points and solubilities, are affected significantly by the presence of the OH group. The boiling point of alcohols is much higher than alkanes with the same number of carbons, due to the hydrogen bonding of the OH group. For example, the boiling point of ethanol is 78°C while ethane has the boiling point of −88°C.

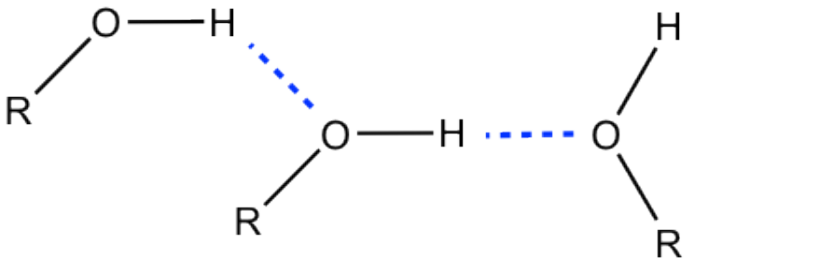


Fig. 1.1d H-Bondings between alcohols

The high polarity of the OH group also contributes to the good solubility of smaller alcohols (up to butanol) in water. As the length of the carbon chain increases, the solubility of alcohol decreases since the size of the hydrophobic potion overrides the hydrophilic potion (refer to **section 2.6 in Book I**).

Name	Structure	Boiling Point (°C)	Solubility in 23
Methanol	CH_3OH	65.0	infin
Ethanol	CH_3CH_2OH	78.5	infin
1-Propanol	$CH_3CH_2CH_2OH$	97.4	infin
1-Butanol	$CH_3CH_2CH_2CH_2OH$	117.3	8.0g / 1
1-Pentanol	$CH_3CH_2CH_2CH_2CH_2OH$	138	2.2g / 1

Table 1.1 Physical properties of some common alcohols

1.1.2 Ethers

Ether is a type of compound that contains an oxygen atom bonded to two carbon atoms. The hydrocarbon groups may be alkyl, alkenyl, vinyl, or aryl. Other than open chain structure, ether may also be in ring structure. Several examples of ethers are shown below. Diethyl ether is an organic solvent and was at one time widely used as an anesthetic agent but was then replaced by other substances due to its slow effect and recovery time, plus its high inflammability. THF is the common polar aprotic solvent, as we learned in **section 7.5 in Book I.**

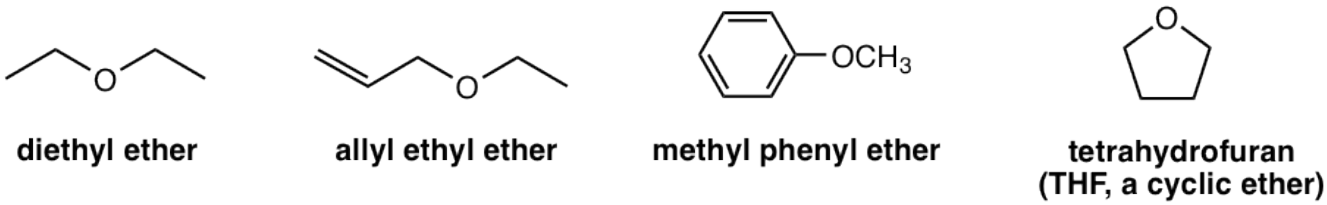


Fig. 1.1e Examples of ethers

The naming of the ether can be referred to in **section 2.4 in Book I**. Simple ethers are named as common name "alkyl alkyl ether" with the alphabetic order of the alkyl groups. For the structure with other groups with higher priorities, ether is regarded as the substituent and named with the "oxy" prefix.

The boiling points of ethers are roughly comparable with those of hydrocarbons of similar molar mass, since the ether group is just slightly polar. As an example, diethyl ether (MM = 74 g/mol) has a boiling point of 34.6 °C, while pentane (MM = 72 g/mol) has that of 36 °C.

1.2 Reactions of Alcohols

Alcohols undergo a wide range of reactions. The understandings and discussions on the reactions of alcohol can be summarized in the following aspects:

- Acidity of the hydrogen atom of the OH group.
- Basicity and nucleophilicity of the oxygen atom of the OH group.
- Conversion of the OH group to a better leaving group (halide, tosylate, etc.) allows substitution or elimination reactions to be followed.

1.2.1 Alcohols as Acids

In the organic acids and bases section in Book I, we have explored the acidities of different functional groups, including alcohols (**section 3.3 in Book I**). The acidities of alcohols are generally similar to that of water, with pKa of 15 ~ 16.

Sterically hindered alcohol is usually less acidic than unhindered alcohol. For example, the pKa of *tert*-butanol is 18, much higher than that of ethanol which is 16. This is due to the different strengths of the solvation effect for alkoxide anions of the two alcohols. For the bulky group, *t*-BuO^-, it is more difficult for solvent molecules to circle around, so the solvation effect is less effective than that of EtO^-. As a result, the *t*-BuO^- is more basic than EtO^-, and *tert*-butanol is more acidic than ethanol.

Fig. 1.2a pKa of t-butanol and ethanol

Sodium or potassium metal, and the metal hydrides (NaH or KH) are common reagents applied in organic synthesis to convert alcohols to the conjugate bases, alkoxide. Refer to the "practical tips for working on S_N1 and S_N2 reactions", **section 7.5 in Book I**.

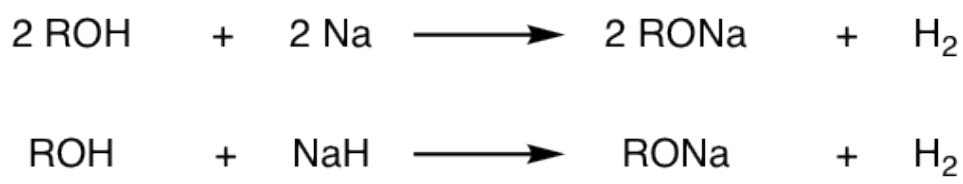


Fig. 1.2b Preparation of alkoxide with sodium or sodium hydride

Alkoxides are often used in organic reactions as either strong bases or strong nucleophiles, depending on the structure of the substrate. Small-size alkoxides, such as methoxide (CH_3O^-) and ethoxide ($CH_3CH_2O^-$), are typically good nucleophiles for S_N2 when react with primary substrates. They are also strong bases for E2 reaction of tertiary substrates. The bulky alkoxide, *t*-BuO–, is a common choice of the bulky base that leads to Hoffmann product in E2 reaction. Refer to **section 8.4 in Book I** for specific examples.

1.2.2 Alcohols as Bases

The oxygen atom of the OH group is weakly basic because of the electron pairs on oxygen. With strong acid present, OH acts as a base and gets protonated.

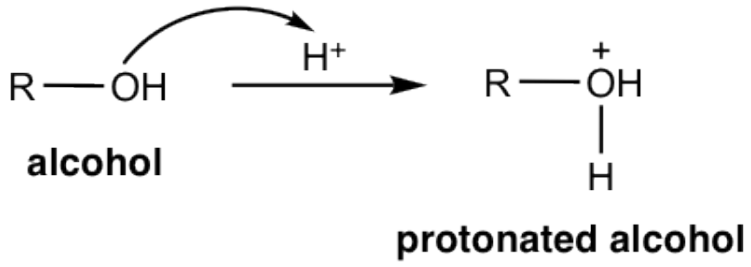


Fig. 1.2c Protonation reaction of alcohol

Protonation of the alcohol converts the poor leaving group OH into a good leaving group H_2O, and the substrate is available for substitution or elimination reactions. The detailed reaction pathway depends on the structure of the alcohol and the reaction condition, as outlined below.

- S_N2 mechanism applies to primary alcohols, when good nucleophiles present, as shown in the example below.

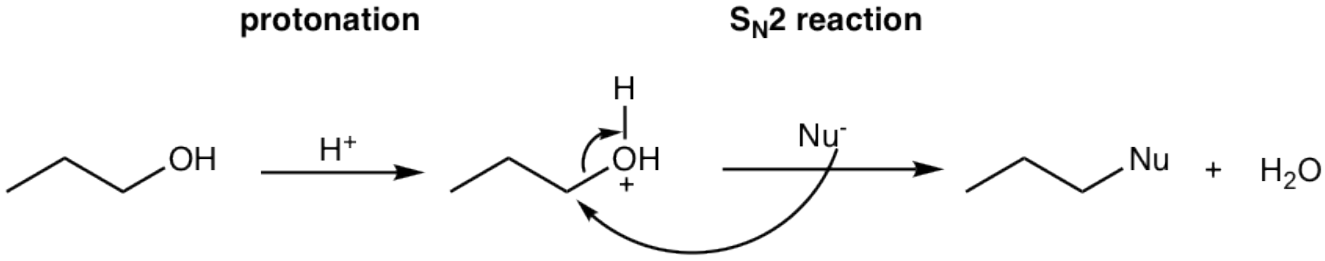


Fig. 1.2d S_N2 reaction of protonated primary alcohol

- Secondary and tertiary alcohols intend to react by the S_N1 mechanism, in which the carbocation intermediate is involved.

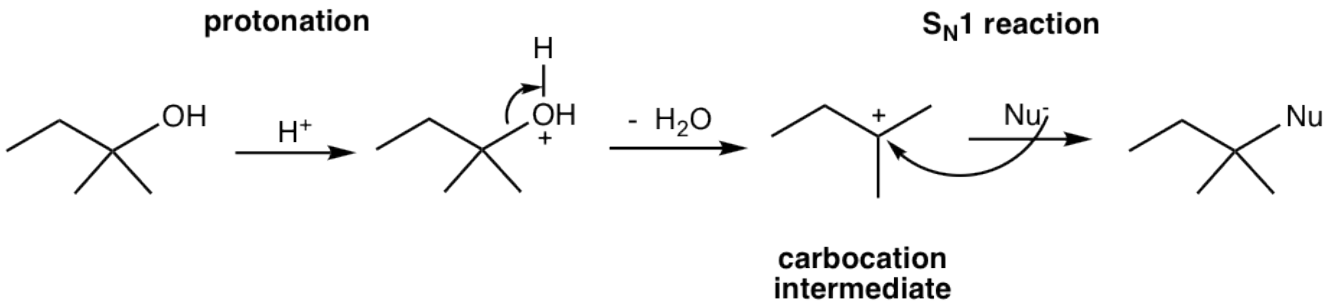
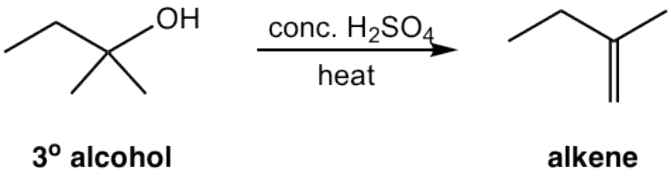


Fig. 1.2e S_N1 reaction of protonated tertiary alcohol

- Elimination (E1) reaction is another option for carbocation intermediate. If no strong nucleophile is present, under high-temperature reaction conditions, E1 is the major reaction pathway that produces alkene. For the following example, when tertiary alcohol is treated with concentration H_2SO_4, with heat, alkene is generated as the product.



Mechanism:

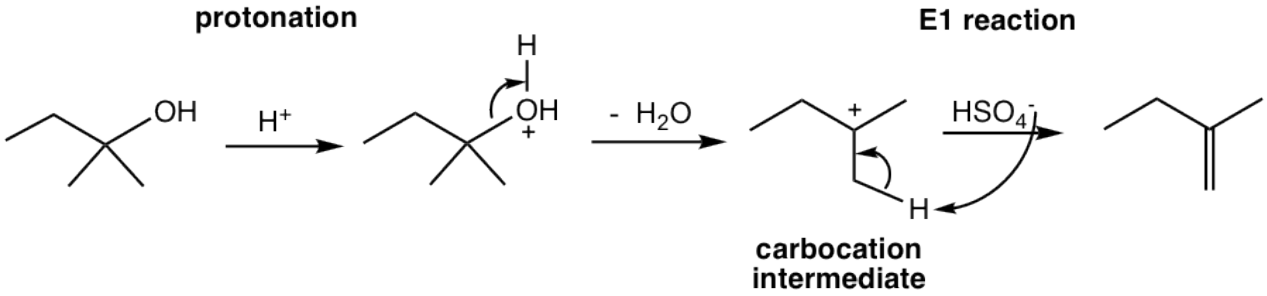


Fig. 1.2f E1 reaction and mechanism of protonated tertiary alcohol

The hydrogen sulfate anion (HSO_4^-) present in the above reaction is a weak nucleophile and does not promote substitution reaction. Under the high temperature, the carbocation loses a proton and becomes an alkene product. You may recognize the above reaction is the **dehydration of alcohol**, which we learned in **section 10.1.2 in Book I**, a method to synthesize alkene.

1.2.3 Conversion of Alcohols into Alkyl Halides

Alcohols also undergo halogenation reactions, that is the conversion of the OH group to halides (Cl or Br). The most commonly applied reagents for such conversions are hydrogen halides (HCl, HBr), phosphorous tribromide (PBr_3), and thionyl chloride ($SOCl_2$), as shown below.

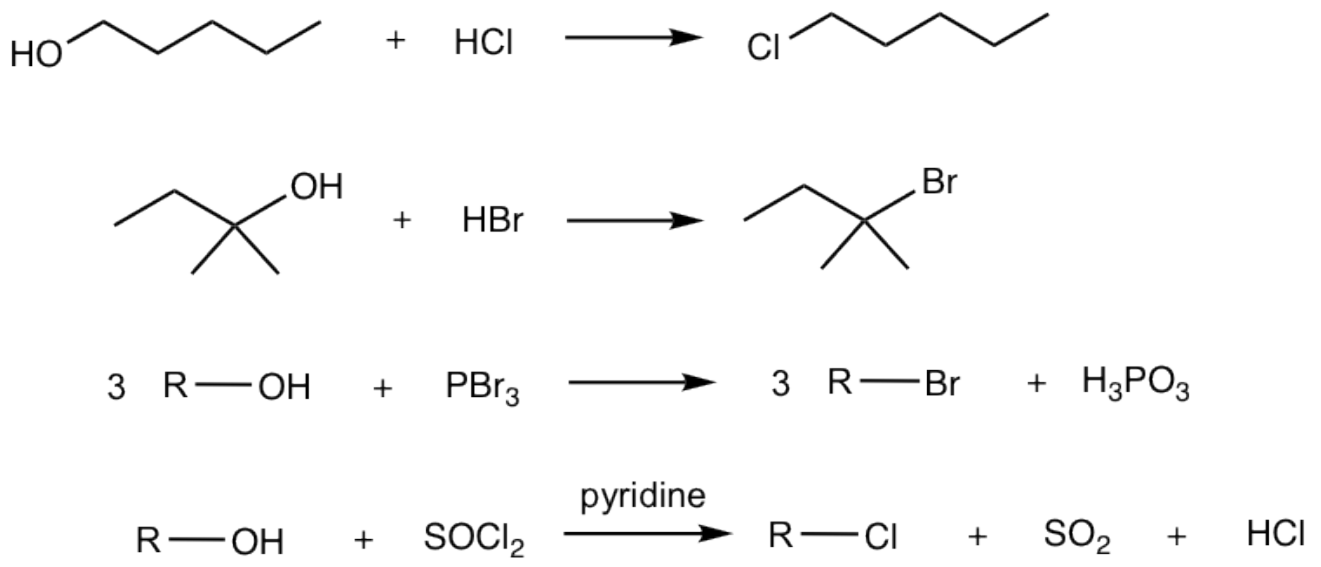


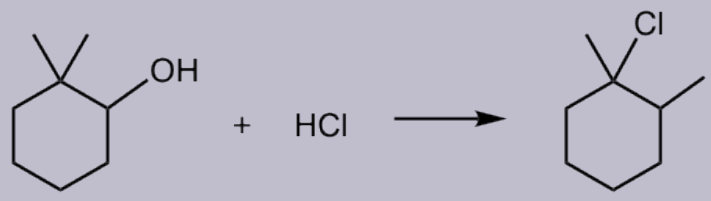
Fig. 1.2g Conversion of alcohols into alkyl halides

Depending on the reagents used in the reaction, the mechanism for halogenations varies a lot. The application of HX involves the multiple-step mechanisms that were just discussed in the last section **1.2.2**. For strong acid HX, X^- is generated after the protonation step, and acts as the strong nucleophile taking part in the following substitution step.

As mentioned in section **1.2.2** carbocation might also undergo elimination (E1) as a competitive mechanism to produce alkene (dehydration of alcohol). The competition between elimination and substitution can be controlled by applying different reaction conditions. The dehydration reaction of alcohol is usually carried in concentrated acid conditions at high temperatures; while the substitution reaction proceeds well in the presence of good nucleophile halide ions (for example Cl^-) and at lower temperatures. However, it is observed often in experiments that a small amount of alkene is present as a side product in the reaction of converting alcohol to an alkyl halide.

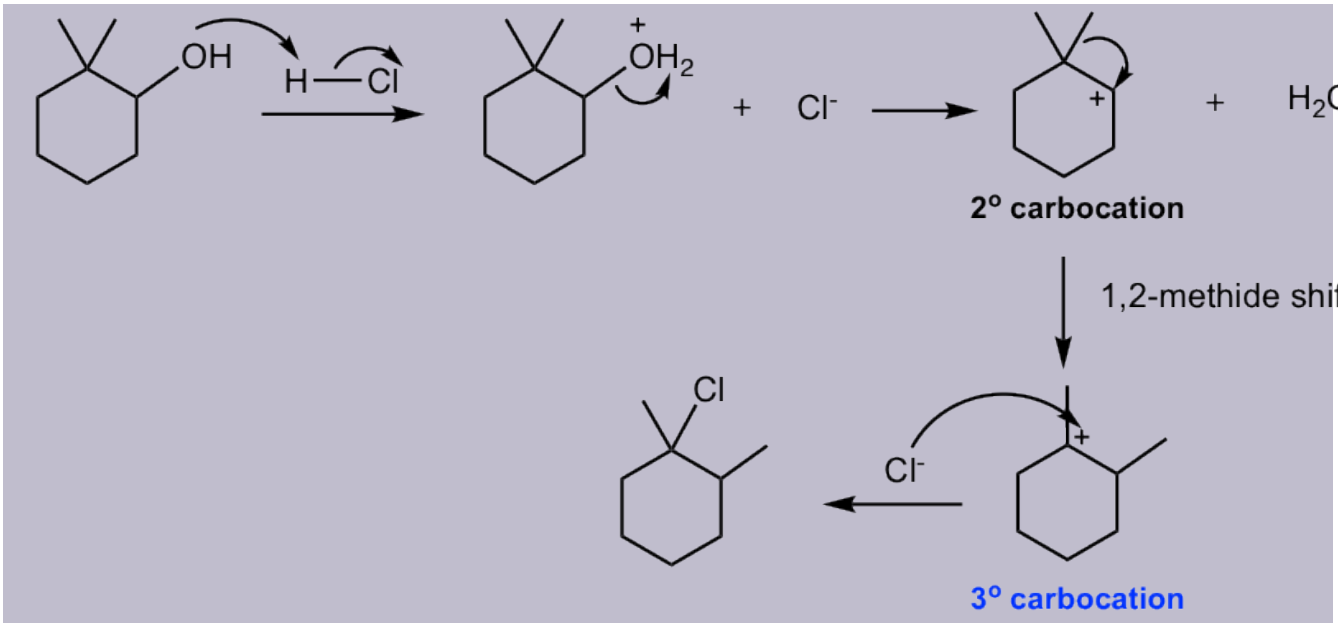
For the reactions in which carbocation is involved in the mechanism, the possibility of rearrangement should also be considered, as illustrated in the following example.

Examples: Propose a mechanism for the following reaction.



Solution:

The carbocation formed initially is a 2° one, and the 1,2-methide shift leads to a 3° carbocation which is more stable. That explains the structure of the final product.



Phosphorous tribromide (PBr_3) and thionyl chloride ($SOCl_2$) are the other widely applied reagents for the conversion of alcohol to alkyl halides, please note a couple of points for the application of these reagents.

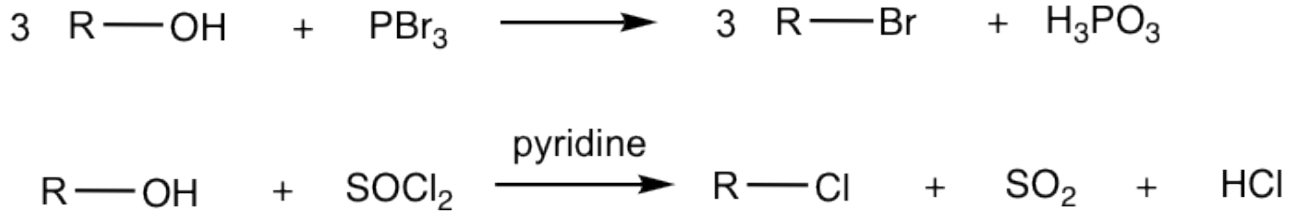


Fig. 1.2h Conversion of Alcohols into Halides with Phosphorous tribromide and thionyl chloride

1. PBr_3 is often used for the transformation of alcohol to the corresponding bromide, while $SOCl_2$ is used for the formation of chloride from alcohol.
2. Both reagents work best for primary and secondary alcohols. The detailed mechanism for the reactions with these reagents will not be covered in this book, however, a note is that no carbocation is involved in the mechanism, and no rearrangements need to be concerned. This is a benefit of using PBr_3 or $SOCl_2$.
3. Amine (pyridine is used most commonly) is usually needed to promote the reaction with $SOCl_2$. A simple understanding is that amine helps to neutralize the side product HCl, thus drawing the equilibrium toward product formation. The detailed mechanism however involves more complicated steps.

1.2.4 Conversion of Alcohols into Tosylate

The reactions of alcohol with acid or hydrogen halide provide two ways of converting the poor leaving group (OH), to a better leaving group, H2O and alkyl halide respectively. Another way for such purpose is the introduction of sulfonate ester from alcohol. The most common sulfonates used are tosylates (p-toluenesulfonate esters, OTs), mesylates (methanesulfonate esters, Oms) and triflates (trifluoromethanesulfonates, OTf). When alcohol reacts with the

appropriate sulfonyl chloride, with the presence of a weak base, for example, pyridine, the sulfonate ester is formed. The weak base here neutralizes the side product HCl and drives the reaction to complete.

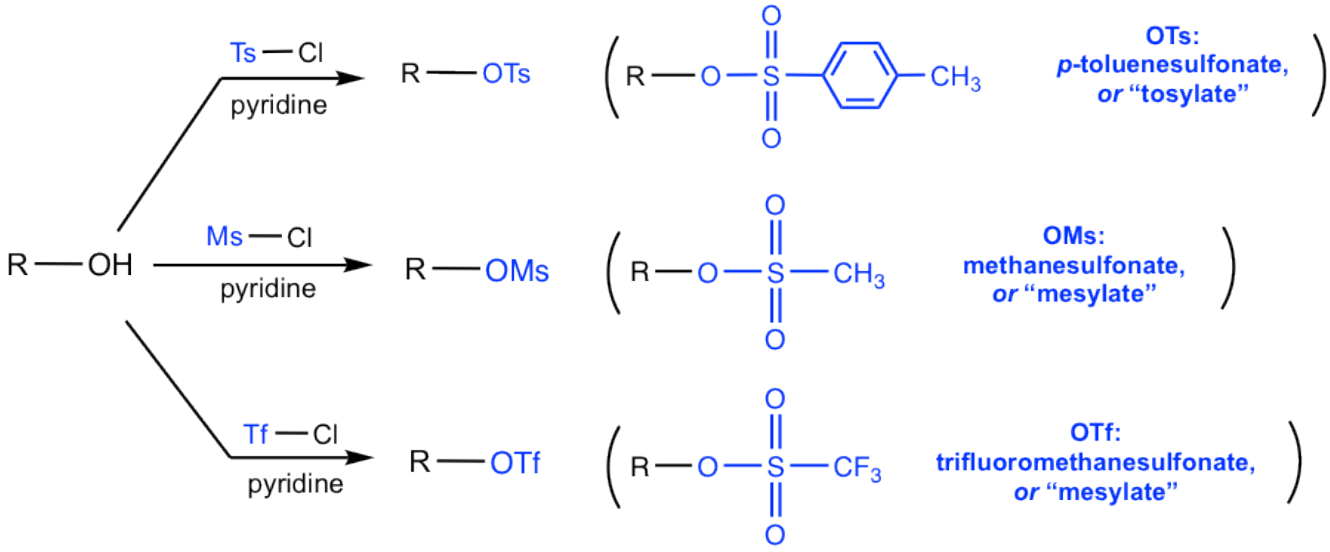


Fig. 1.2i Conversion of alcohols into sulfonate esters

These sulfonate esters are conjugated bases of strong organic sulfonic acids (all with pKa in the negative range as shown in Fig. 1.2j), therefore they are very weak bases and as a result excellent leaving groups.

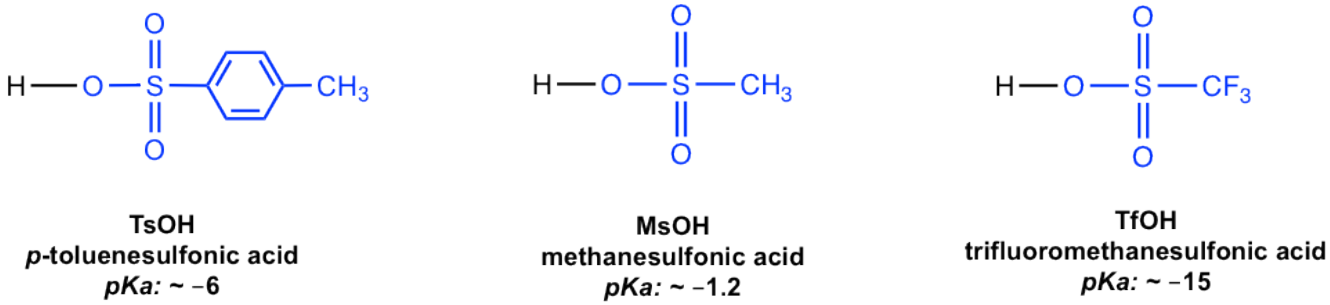
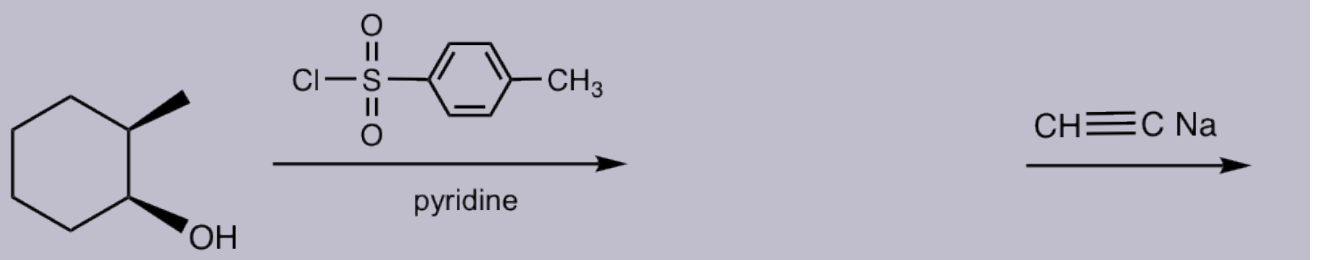


Fig. 1.2j Structures and acidity of some sulfonic acids

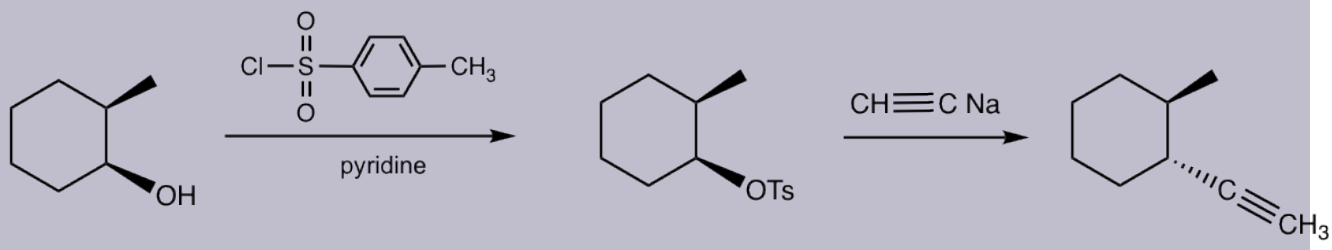
The resulting sulfonates are good substrates for substation (S_N2) reactions and the overall 2-step reaction sequence provides a good synthesis strategy to convert alcohol into a variety of functional groups, for example, ether, cyanide, etc. Such applications have been discussed in the "Extra topic of nucleophilic substation reaction" in **section 7.6.3 in Book I**.

For alcohols with chirality centers on the carbon, introducing sulfonate ester to alcohol will not affect the stereochemistry of the chirality centers. This represents a benefit of using this strategy in the synthesis. The retention of the configuration is because the C-O bond is not involved in the formation of the sulfonate ester, therefore the stereochemistry of the alcohol carbon is not affected in this step. This strategy hence provides a way to synthesize the stereo-specific product as shown in the following example.

Example: Show the product of the following reactions with stereochemistry included.



Solution:



1.2.5 Oxidation of Alcohols

Primary and secondary alcohols are oxidized into the functional groups with higher oxidation states (refer to Fig. 10.7a in **section 10.7 in Book I**), when reacting with an oxidizing agent. Specifically, primary (1°) alcohols can be oxidized to aldehydes, which can be further oxidized to carboxylic acids, and secondary (2°) alcohols are oxidized to ketones. Tertiary (3°) alcohols cannot be oxidized. It also makes sense that the functional group can also be reduced from a higher oxidation state to a lower state with a reducing agent applied, and that will be covered in later section **1.4.2**.

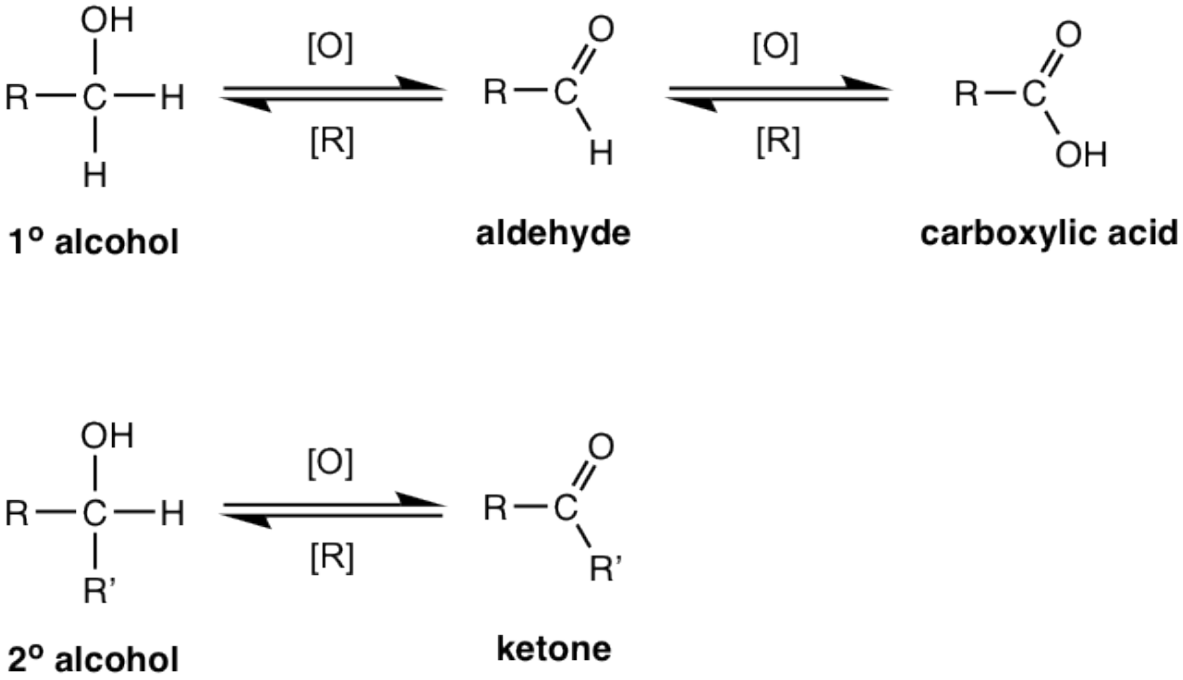


Fig. 1.2k The relative oxidation state of some common organic functional groups

The most common oxidizing agents are the chromium (VI) reagents, such as CrO_3, and H_2CrO_4. Such Cr (IV) reagents are also known as Jones reagents, that are prepared by adding CrO_3 or Na_2CrO_4 to dilute sulfuric acid. The reaction can be readily handled by adding the solution of Jones reagent to aldehyde or ketone. However, the environmental hazard of Cr(IV) reagent limits its application.

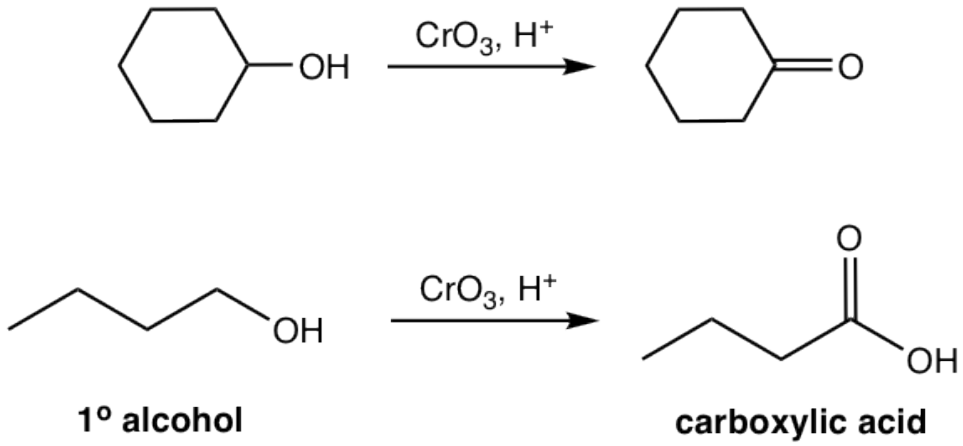


Fig. 1.2l Oxidation of alcohols with chromium (VI) reagents

A problem with using the Cr (IV) reagent is that primary alcohols are oxidized to carboxylic directly, instead of aldehyde, due to the strong oxidizing ability of the reagent. A milder oxidizing agent, pyridinium chlorochromate (PCC), can be used instead to produce aldehyde from primary (1°) alcohol. PCC is the salt formed between CrO_3, pyridine, and HCl.

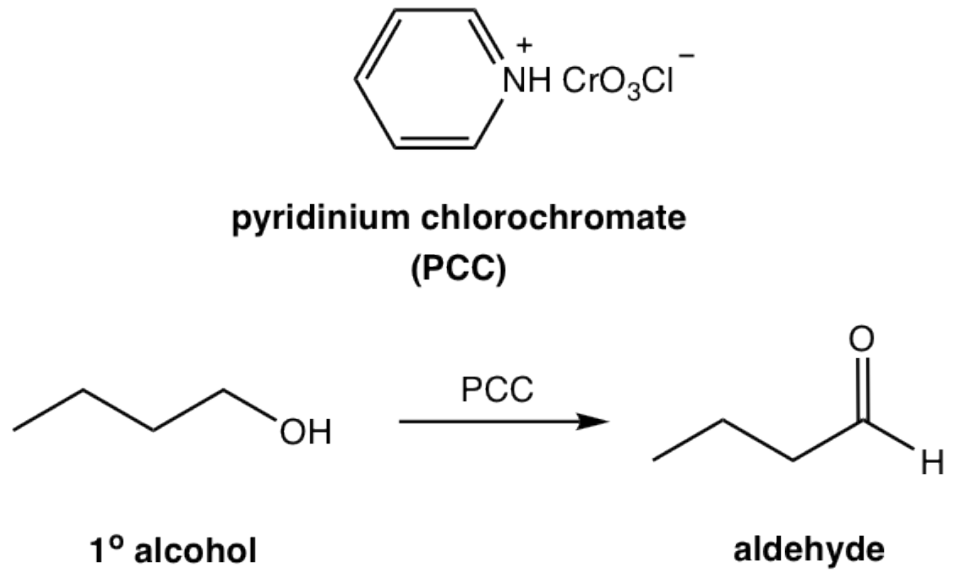


Fig. 1.2m Oxidation of alcohols with pyridinium chlorochromate (PCC)

Another strong oxidizing agent, potassium permanganate ($KMnO_4$), can also be used to oxidize primary or secondary alcohol, and produces carboxylic acid or ketone as the final product respectively. A note for using $KMnO_4$ with primary alcohol is that since the reaction usually is carried out in a basic solution, another acidification step is necessary to produce carboxylic acid as the product.

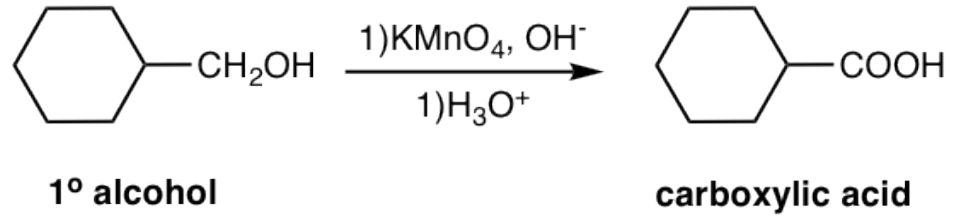


Fig. 1.2n Oxidation of alcohols with potassium permanganate

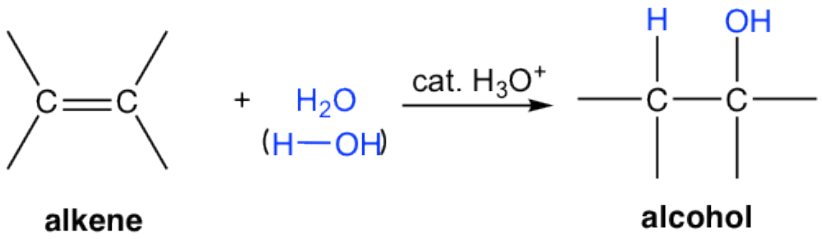
1.3 Synthesis of Alcohol from Alkenes

For organic synthesis purposes, alkenes are the common starting materials to produce alcohols. In the sections of "Reactions of Alkenes" in Book I, several methods have been discussed for the synthesis of alcohols from alkenes, including the acid-catalyzed hydration of alkene (**section 10.3 in Book I**), oxymercuration–demercuration of Alkenes and hydroboration–oxidation of Alkenes (**section 10.6 in Book I**). These methods are summarized and compared in the following table.

Synthesis of alcohols from alkenes

Acid-catalyzed hydration of alkene

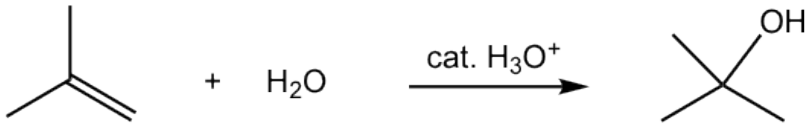
General reaction:



Notes:

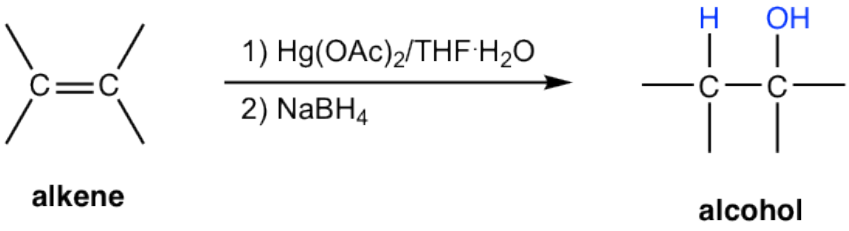
- Follow Markovnikov rule
- Rearrangement might occur because th intermediate involved

Example:



Oxymercuration–Demercuration of Alkenes

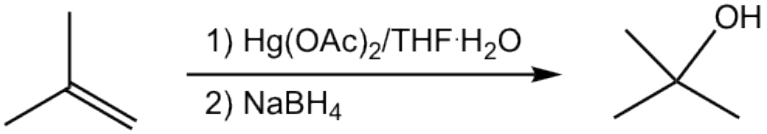
General reaction:



Notes:

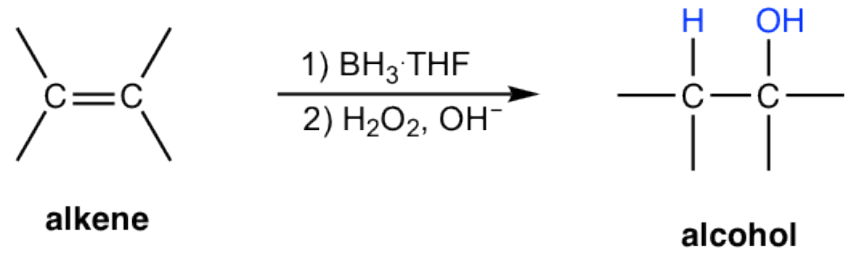
- Follow Markovnikov rule
- No Rearrangement

Example:

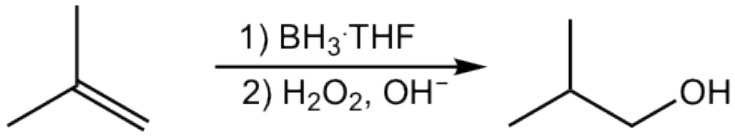


Hydroboration–Oxidation of Alkenes

General reaction:



Example:



Notes:

- Follow **anti**-Markovnikov r
- Syn-addition

Table 1.2 Synthesis of alcohols from alkenes summary

1.4 Synthesis of Alcohols from Carbonyl Compounds

Alcohols can also be prepared from some carbonyl compounds, i.e., the compounds containing the carbonyl group, for example, aldehyde, ketone or ester. This process involves a very important type of reaction and a group of powerful reagents, organometallic compounds, that are brand new to us.

Our journey in this topic will start with the structure features of carbonyl compounds, followed by the introduction of the new reagents, and then take a deep insight into the reactions. Other than the reactions that will be covered in this section, there will be more chapters (chapters 2, 6, 7, and 8) later to explore the properties and reactivities of carbonyl compounds.

1.4.1 Structure Features and Reactivity of Carbonyl Group Compounds

The carbonyl group is the key and common structure unit in all carbonyl compounds (refer to **section 2.3 Book I**).

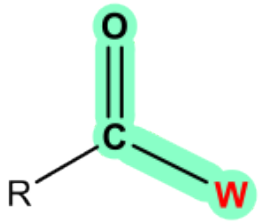


Fig. 1.4a General structure of carbonyl compounds

The central carbon atom in the carbonyl group is sp^2 hybridized, therefore all the three atoms attached to the central carbons are in the same plane. The bond angles between any two bonds are about 120 and the overall shape can be described as trigonal planar.

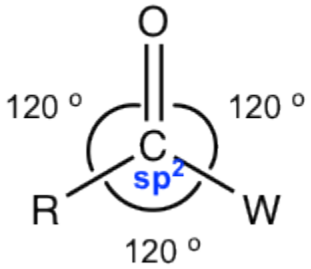


Fig. 1.4b Trigonal planar shape of carbonyl group

The C=O bond is highly polarized because of the electronegativity difference between the carbon atom and the oxygen atom. The electron density is attracted strongly to the O side because of the high electronegativity of the oxygen atom.

Therefore, the oxygen atom bears a substantial negative charge and the carbon atom bears a substantial positive charge, which can be represented by the following structures.

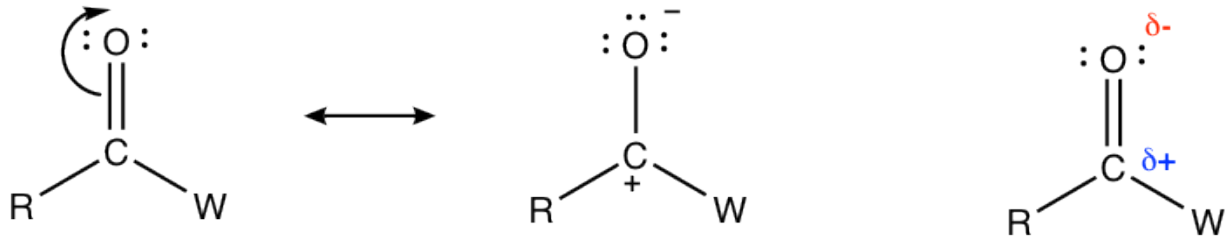


Fig. 1.4c Resonance structure and bond polarity of the carbonyl group

Because of the strong polarity of the C=O bond, carbonyl compounds usually exhibit a large dipole moment value. The example of acetone is shown in Fig. 1.4d.

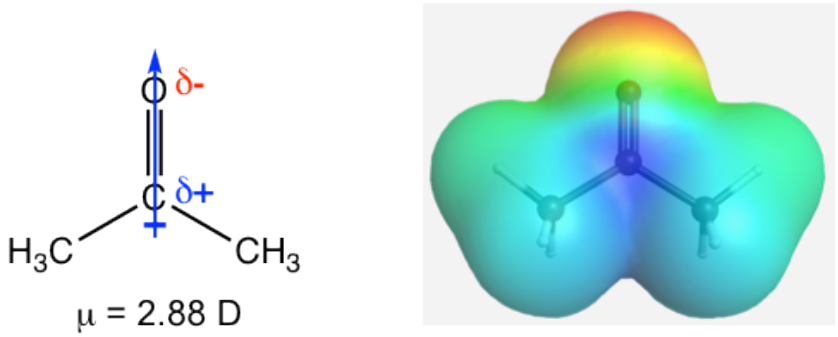


Fig. 1.4d Dipole moment and electrostatic potential map of acetone. (In the electrostatic potential map, the red color indicates the partial negative charge on the oxygen atom, and the blue color indicates the partial positive charge on the carbon atom.)

The partial charge separation on the atoms of the carbonyl group plays a critical role in the reactivity of carbonyl compounds.

Because of the partial positive charge on the carbon atom, the carbonyl group is highly susceptible to **nucleophilic** attack (Fig. 1.4e). For aldehydes and ketones, the carbonyl compounds we will focus on in this section,**nucleophilic addition is one of the most important reactions.**

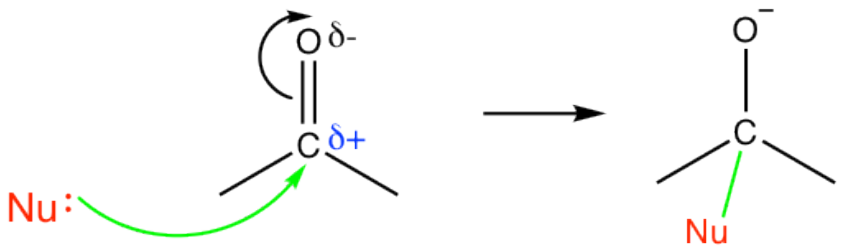


Fig. 1.4e Nucleophilic attack on carbonyl group

In the above nucleophilic attack, the electron pair (negative charge) of the nucleophile is attracted by the partial positive charge on the carbon atom, and a new bond is formed when the nucleophile adds to the carbonyl carbon. As a result, the electron pair in the C=O double bond shifts to the oxygen atom to generate an oxide anion. With the reaction taking place, the structure of the carbon atom changes from sp^2 hybridization with a trigonal planar shape to sp^3 hybridization with a tetrahedral shape.

The simple idea of positive charged (or partially positive charged) species attracted by and reacts with negative charged (or partially positive charged) species is the underlying theory for understanding a lot of different reactions. Keeping this idea in mind is very useful! The nucleophilic addition here is a typical example of this theory, and so are the S_N1/S_N2 reactions we learned in Book I.

Now we understand that the carbonyl carbon is ready to react with nucleophiles, in the following sections we will introduce a couple of metal reagents, metal hydrides and organometallic reagents, the new reagents that act as nucleophiles.

1.4.2 Reduction of Carbonyl Compound by Metal Hydrides

For metal hydrides, the hydride ion (H^-) acts as a nucleophile to attack the carbonyl carbon. The most commonly applied metal hydrides are lithium aluminum hydride (LAH, with the formula of $LiAlH_4$) and sodium borohydride ($NaBH_4$) with structures given here.

Fig. 1.4f Structure of lithium aluminum hydride and sodium borohydride

The common feature of these two reagents is that they both have hydride anion (H^-) that acts as a nucleophile to react with the carbonyl group. However, they also show different reactivities. Lithium aluminum hydride is a very strong reducing agent that can reduce most carbonyl compounds including carboxylic acid, ester, aldehyde, and ketone. Sodium borohydride could only be used to reduce aldehyde and ketone because of its lower reactivity.

On the other hand, the reaction conditions required for handling the two reagents are also different due to the reactivity difference. As a side effect of the high reactivity, LAH also reacts violently with protic solvents that contain protons, such as water and alcohol. Anhydrous diethyl ether (Et_2O) is therefore the solvent that is commonly used for LAH reduction, with great care being given to avoid the presence of any moisture, as shown in the general reactions in Fig. 1.4g.

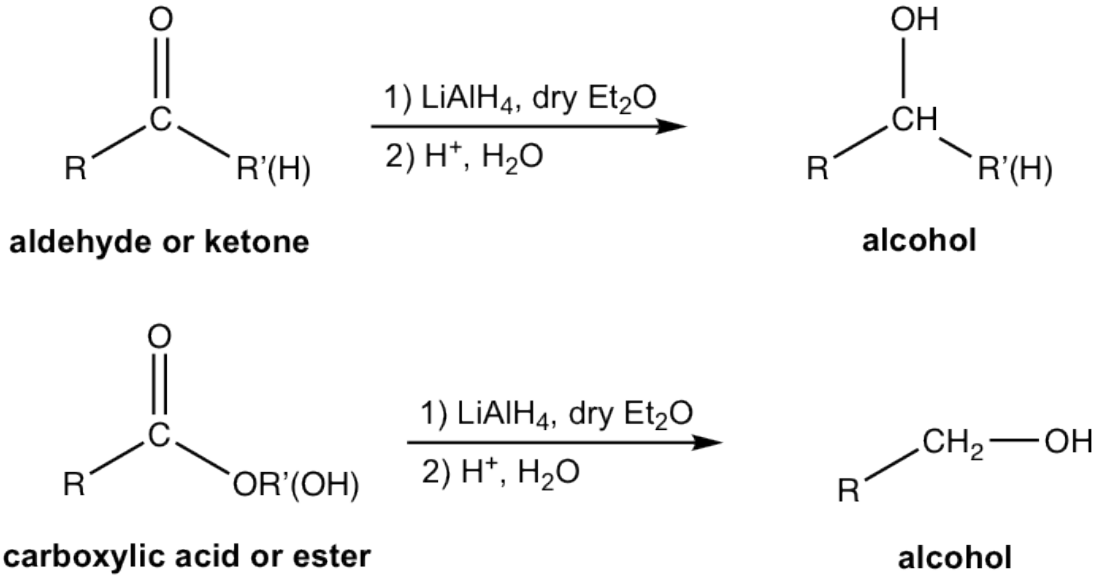


Fig. 1.4g Reduction of carbonyl compound by $LiAlH_4$

When all of the LAH has been consumed, dilute acid is added to neutralize the salt. The last step is usually called the "acidic work-up" step. Please note that the two steps must shown as step 1) and step 2) separately in proper order, which means that after the reaction with LAH is completed in step 1), acid will be added as the second step to finish the whole process.

Sodium borohydride, on the other side, is a less powerful reducing agent and can be used safely with alcohol as the solvent.

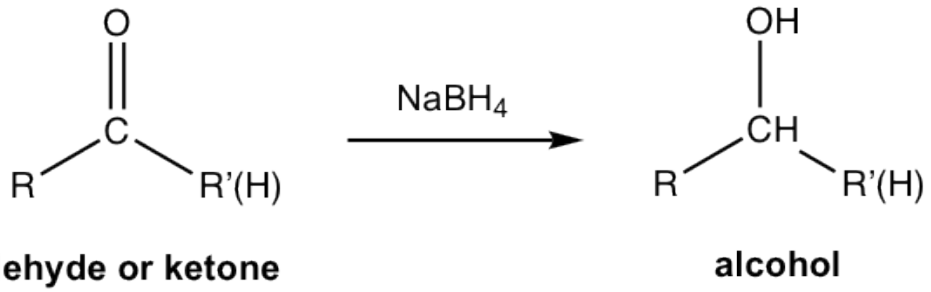


Fig. 1.4h Reduction of aldehyde/ketone by $NaBH_4$

The above reactions represent effective ways to synthesize alcohol. Because alcohols are in a lower oxidation state than carbonyl compounds, they are reduction reactions. The reduction of aldehyde produces primary alcohol, the reduction of ketone produces secondary alcohol, and the reduction of acid/ester by $LiAlH_4$ produces primary alcohol only.

The mechanism for the reduction of aldehyde/ketone by $NaBH_4$ is shown in Fig. 1.4i. The overall mechanism is an addition to the carbonyl group, which represents a good example of the reactivity of the carbonyl group shown in Fig.1.4e. Hydride ion (H^-) first acts as a nucleophile to attack the carbonyl carbon that bears a partial positive charge, the resulting oxide is protonated by the solvent to give alcohol as the final product. Such a reaction is also called a **nucleophilic addition** reaction.

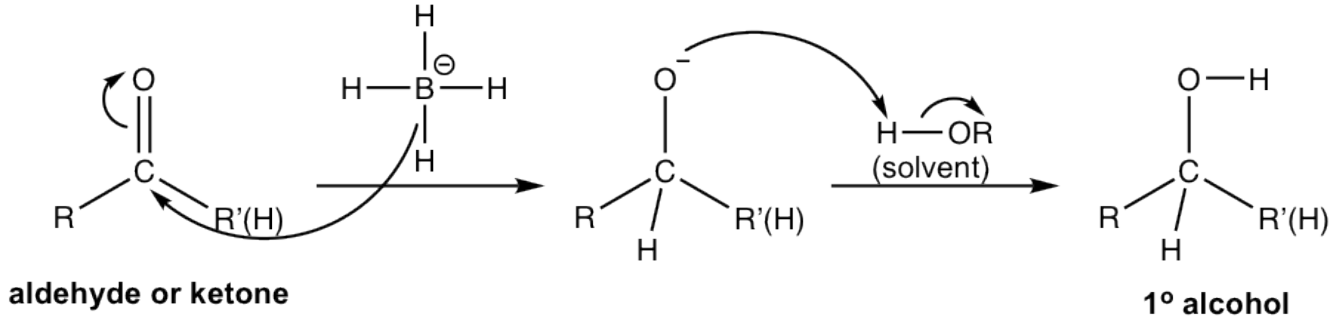


Fig. 1.4i Mechanism for the reduction (nucleophilic addition) of aldehyde/ketone by $NaBH_4$

$LiAlH_4$ reduces aldehyde/ketone by the same mechanism. The mechanism for the reduction of carboxylic acid/ester by $LiAlH_4$ will be discussed in Chapter 7.

1.4.3 Organometallic Compounds

Another type of reagent that acts as a nucleophile is called the organometallic compound.

Carbon element is the key element in all organic compounds. In the organic structures we have learned so far, covalent bonds are always formed between the carbon element and other non-metal elements, such as carbon, hydrogen, oxygen, sulfur, phosphorous elements, etc. The carbon element can also bond with metal elements, and that is the key feature of this new type of compound: organometallic compounds.

An organometallic compound is a type of compound that contains carbon-metal bonds.

Because metals are usually less electronegative than carbon, the carbon-metal bond is polar with the carbon element bearing the partial negative charge, and the metal element bearing the partial positive charge. (pg 556)

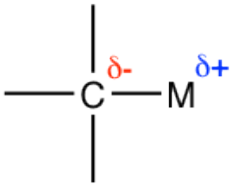


Fig. 1.4j Carbon – metal (C-M) bond in an organometallic compound

We will focus on the properties and applications of the two most common organometallic compounds: organolithium and organomagnesium compounds in this section.

Organolithium Compounds

The general way of preparing organolithium compounds is by reacting lithium metal with alkyl halide. These reactions are usually carried out in dry ether solvent (Et_2O or THF) to avoid the side reaction between moisture with the resulting organolithium compounds.

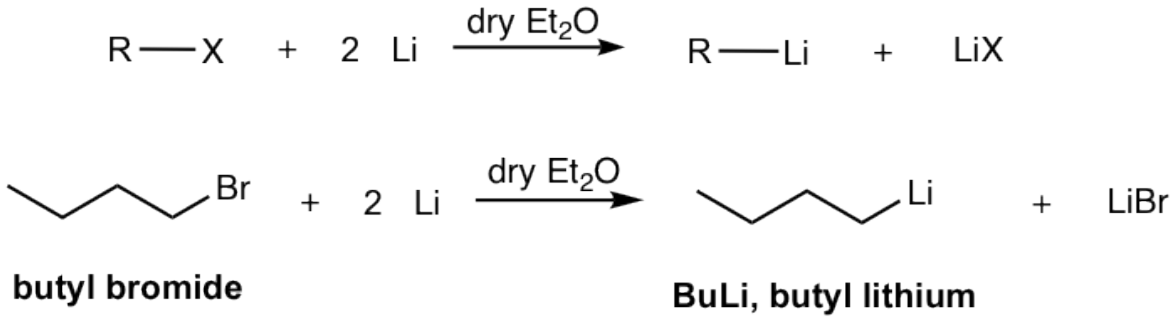


Fig. 1.4k Preparation of organolithium compounds

The name of organolithium compounds starts with the name of the alkyl group, followed by "lithium". In the above example in Fig. 1.4k, the compound with formula BuLi is named butyl lithium.

Organomagnesium Compounds (Grignard Reagents)

The reaction between organic (alkyl or aryl) halide and magnesium metal in dry ether solvent generates organomagnesium compounds, which are commonly called **Grignard Reagents**. The reagents were first discovered by

French chemist Victor Grignard in 1900. Grignard received the Nobel Prize in 1912 for this great discovery that has important applications in organic synthesis.

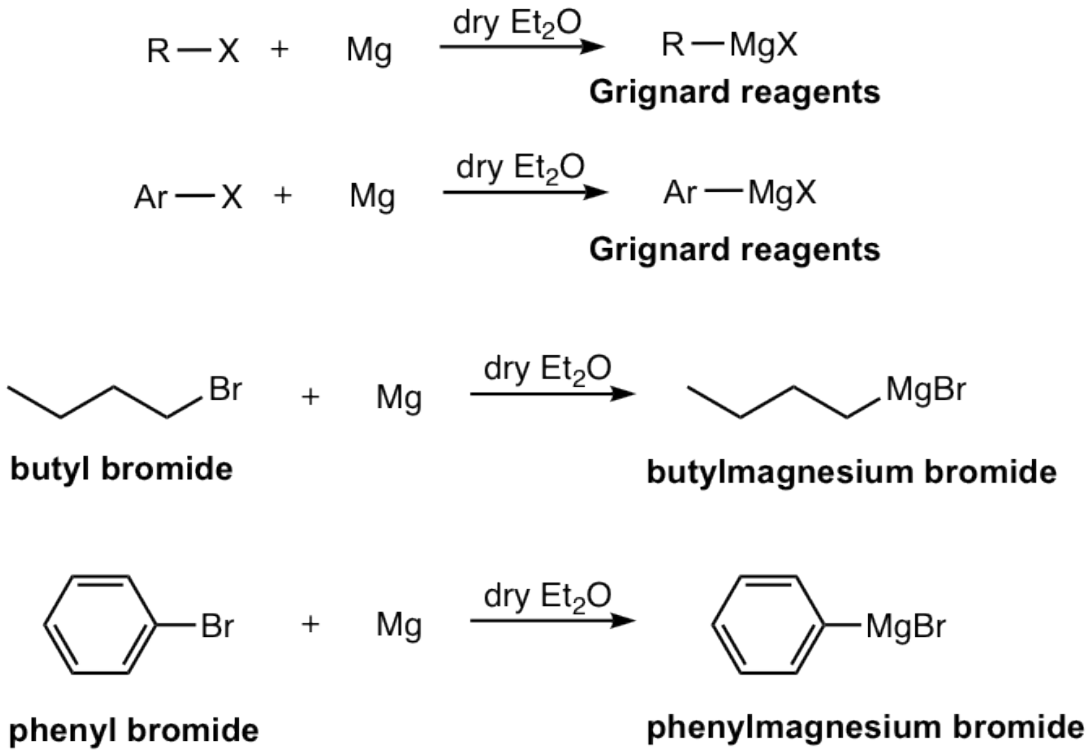


Fig. 1.4l Preparation of Grignard reagent: general equation and specific examples

Grignard reagents can be prepared from both alkyl halide and aryl halide (as shown in Fig. 1.4l), which covers a broader structure scope than lithium reagents. The order of reactivity for halides is RI > RBr > RCl. Alkyl or aryl bromides are used most commonly because of the median level reactivity. Grignard reagents are named "alkyl"+"magnesium"+"halide".

The mechanism for the formation of Grignard reagents is complicated and debatable, with the possible involvement of radicals. Although the actual structures could be more complex, the general formula of Grignard reagent is usually represented in a simplified way as RMgX, with Mg inserts between the carbon and the halogen.

1.4.4 Reactions of Organometallic Compounds with Carbonyl Compounds (for Alcohol Preparation)

The reactivities of these two organometallic reagents can be more easily understood if they are ***regarded*** as the structures involving carbanion and the metal cation, although the actual bonds are not completely ionic.

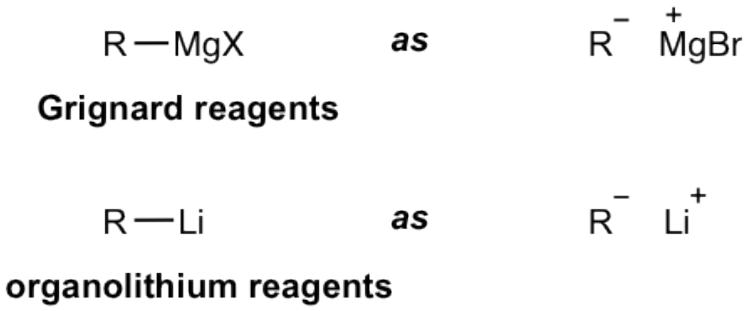


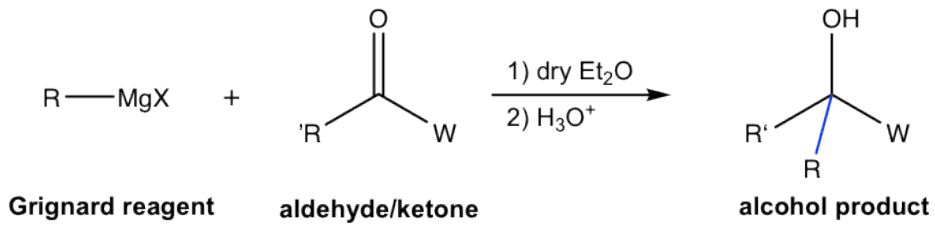
Fig. 1.4m Simplified way to represent the structures of Grignard reagents and organolithium reagents

As discussed earlier (Fig. 1.4e) the carbon atom in the carbonyl group is highly susceptible to nucleophilic attack. The carbanions in these two organometallic compounds, with electron pair and negative charge, are strong nucleophiles that are ready to attack the carbonyl carbon. As a result, the most important synthetic applications of these two organometallic compounds are those in which they react as nucleophiles and attack the carbonyl group.

Grignard Reactions

Let's start with the Grignard reagents. The reaction and mechanism of Grignard reagent with carbonyl compound are shown in Fig. 1.4n. Two steps are involved in the general mechanism. First, the carbonation (R^-) of the reagent acts as a nucleophile to attack the carbonyl carbon, a new bond is formed and the π electron pair of the carbonyl group moves to the oxygen atom to form an intermediate oxide with a tetrahedral shape. In the second step (the work-up step), the oxide is protonated with acid to produce the neutral alcohol product, together with MgX_2 (the inorganic side product). Similar to the reaction conditions for $LiAlH_4$, the two steps must be shown separately with proper order on the overall reaction arrow (Fig. 1.4n).

General equation for Grignard reaction



General Mechanism for Grignard Reaction

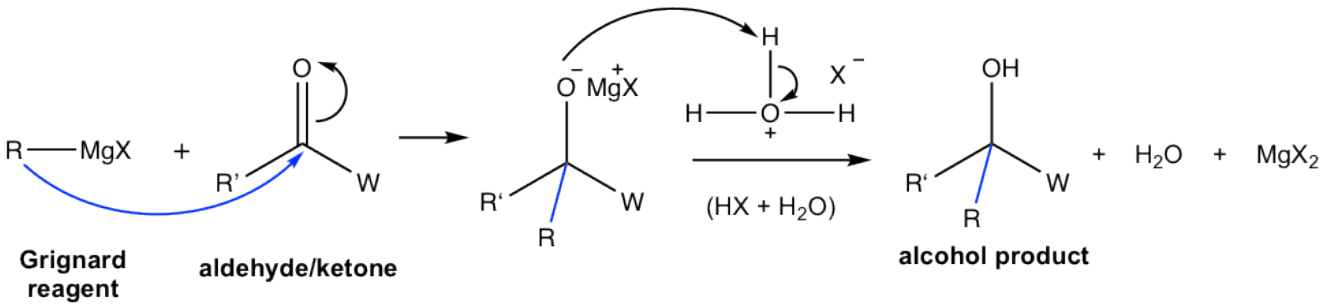


Fig. 1.4n General equation and mechanism for Grignard Reaction

Generally speaking, alcohols are obtained as products of the reaction between Grignard reagents and carbonyl compounds. Depending on the structure of specific carbonyl compounds employed, alcohols with different categories (1°, 2°, or 3°) are formed as summarized in Table 1.3 explicitly. Please note that the Grignard reagent reacts with ester as well, to produce the 3°-alcohol. Since ester reacts with two equivalents of Grignard reagents, there are two identical alkyl groups present in the 3°-alcohol both come from the Grignard reagent.

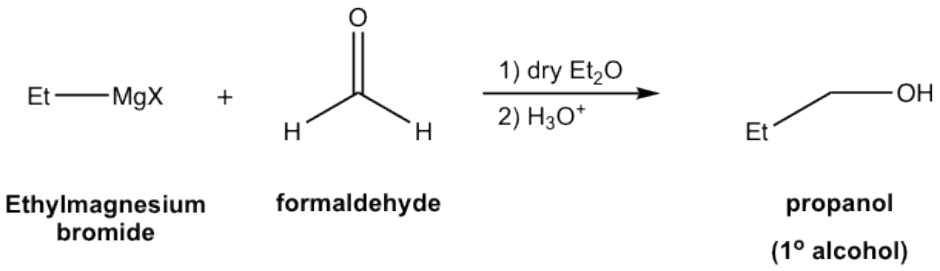
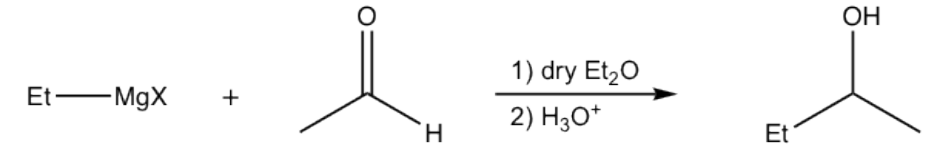
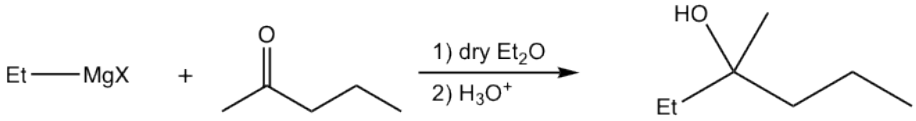
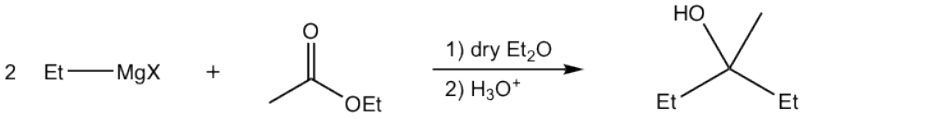
Carbonyl Compound	Product	Specific Example
Formaldehyde	**1°** (primary) alcohol	 **Ethylmagnesium bromide** **formaldehyde** **propanol (1° alcohol)**
Other aldehydes	**2°** (secondary) alcohol	 **Ethylmagnesium bromide** **Acetaldehyde** **2-butanol (2° alcohol)**
Ketones	**3°** (tertiary) alcohol	 **Ethylmagnesium bromide** **2-pentanone** **3-methyl-3-hexanol (3° alcohol)**
Esters	**3°** (tertiary) alcohol **with two identical substituents**	 **Ethylmagnesium bromide (2 equiv.)** **Ethyl acetate** **3-methyl-3-pentanol (3° alcohol, with two identical Et groups)** **The mechanism for Grignard reaction with ester does not fit the mechanism in Fig. 1.4n. It will be covered in detail in section 7.8.2.**

Table 1.3: Alcohol Products by Grignard Reaction of Different Carbonyl Compounds

Special Note: Grignard Reaction of Carbon Dioxide CO_2

Carbon dioxide is not a carbonyl compound. However, the C=O double bond in CO2 does undergo the Grignard reaction in a similar way as other carbonyl compounds and produces carboxylic acid as the product. This is a useful method for the preparation of acids (more discussions about acids in **chapter 7**).

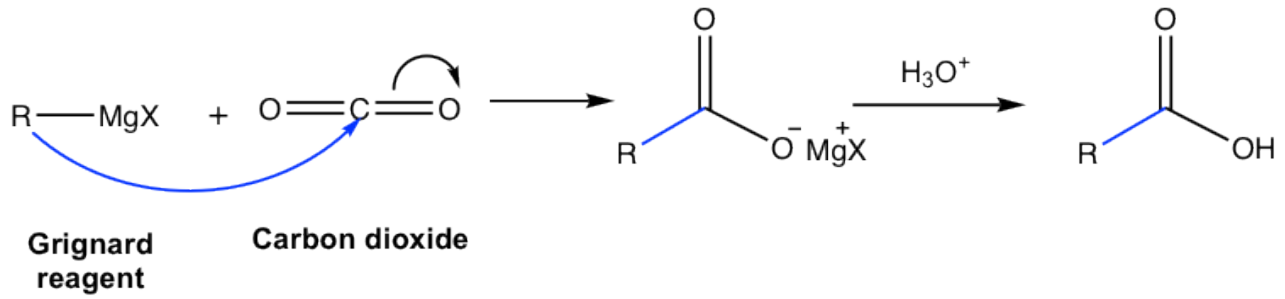


Fig. 1.4o Reaction of Grignard reagent with carbon dioxide to prepare carboxylic acid

Grignard reactions provide opportunities to build larger molecules, this is exactly what chemists are working for in organic synthesis, to synthesize more complicated molecules with more carbons. As a result, the Grignard reaction is a very useful reaction and has been applied broadly in organic synthesis.

Organolithium Reactions

Organolithium reagents (RLi) react with aldehyde/ketone in the same way as Grignard reagents and provide an alternative method for alcohol preparation. While organolithium reagents are more reactive, they are more difficult to handle, and more strict dry reaction conditions are required.

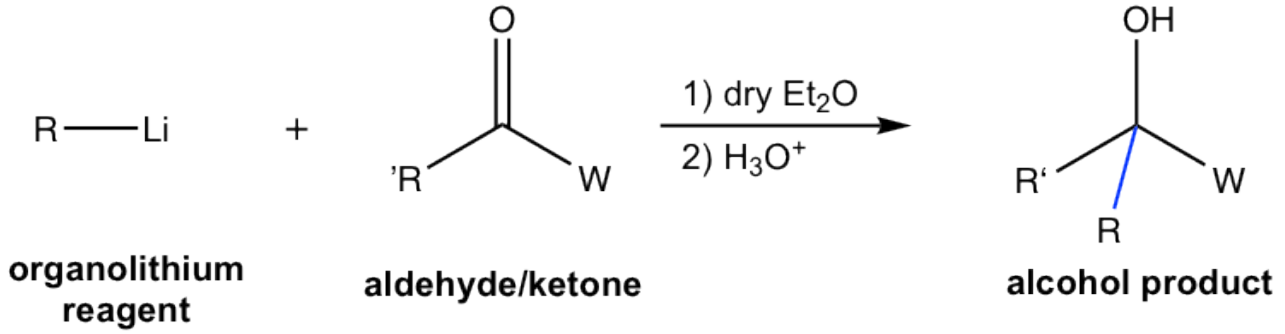


Fig. 1.4p General equation for the reaction of organolithium reagents with aldehyde and ketone

1.4.5 Synthesis Design of Grignard Reactions for Preparation of Alcohols

The diversity and good compatibility of the Grignard reaction allow us to synthesize alcohol with almost any structure. To design the synthesis, we need to choose the proper Grignard reagent and the proper carbonyl compound by examining the structure of the desired alcohol, and applying the retrosynthesis analysis strategy (**section 9.6 in Book I**). There might be more than one reasonable way to achieve the target in many cases.

Before we start the synthesis route designing, let's first examine a Grignard reaction (the 3rd example, the synthesis of 3-methyl-3-hexanol, in **Table 1.3**) in more detail and obtain an in-depth understanding of what's going on in the reaction.

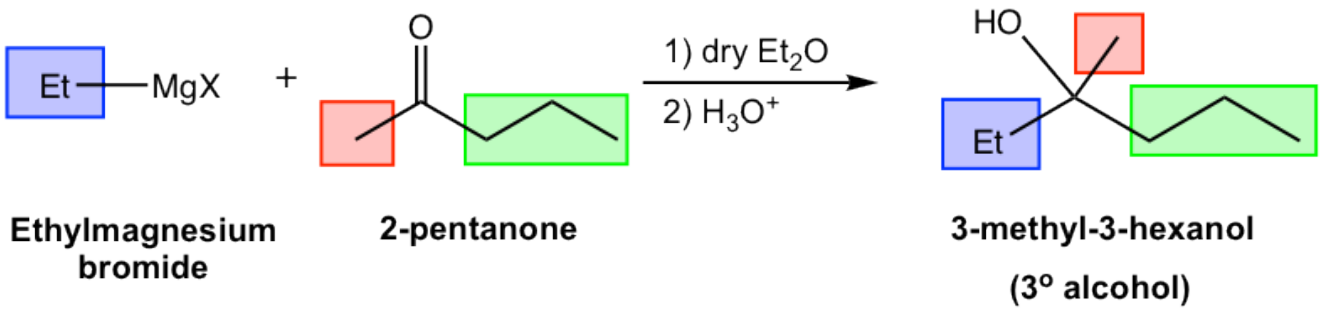


Fig. 1.4q Color-coded analysis for synthesis of 3-methyl-3-hexanol by Grignard reaction

For the above example (Fig. 1.4q), the alkyl groups in both reactants and product are highlighted with different colors for your reference. In the tertiary (3°) alcohol product, **the red and green groups come from ketone, and the blue group comes from the Grignard reagent**. Such a trend can be further visualized in the general equation of the Grignard reaction below in Fig. 1.4r.

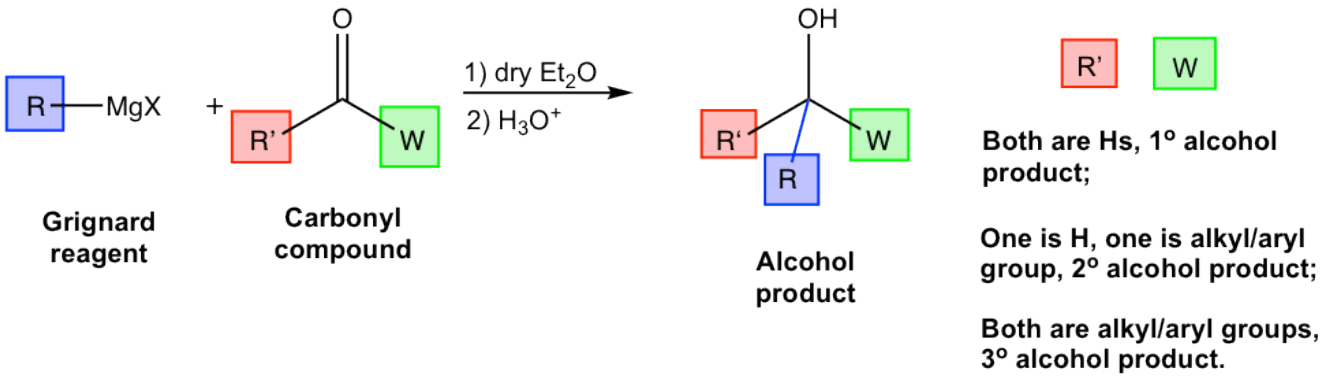


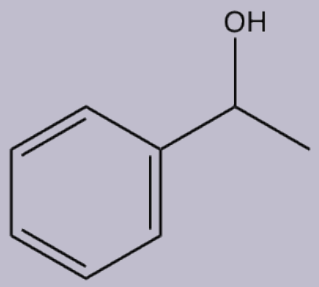
Fig. 1.4r Color-coded analysis for general Grignard reaction

For the three groups bond on the alcohol carbon in the product, one (**blue**) comes from the Grignard reagent, and the other two (**red** and **green**) come from the carbonyl compounds. Depending on the two (**red** and **green**) groups from the carbonyl compounds are either both hydrogens, one hydrogen and one alkyl/aryl group, or both alkyl/aryl groups, the resulting product can be 1°, 2°, or 3° alcohol respectively.

This is a very important and useful trend that can be applied in synthesis design. By analyzing the three groups (or hydrogens) involved in the alcohol product, we can decide what reactants to start with. Theoretically speaking, there is no restriction about which groups come from carbonyl compounds or Grignard reagents, and there are usually multiple ways to synthesize a product. However, if any restrictions/requirements are given in a question, that limits your choice to one possible way. Let's take a look at a couple of examples below for illustration.

Example A:

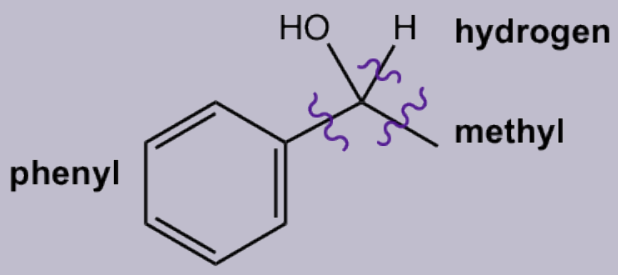
Design a Grignard synthesis of the following compound:



Analysis:

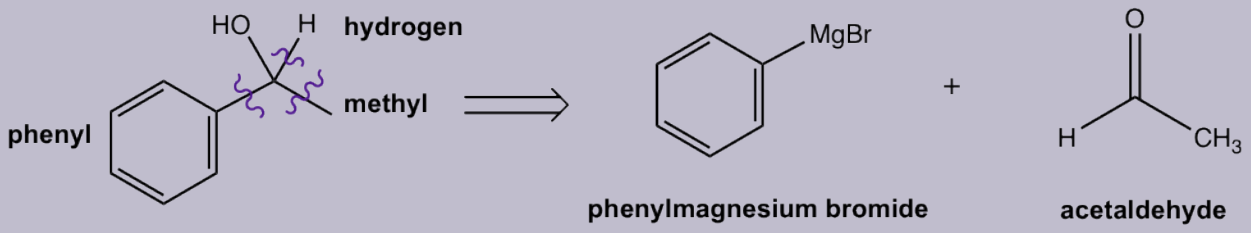
Step 1: This is a 2° alcohol, so one of the three groups bond on the alcohol carbon is hydrogen.

Step 2: Decide the other two groups connected to the alcohol carbon by cutting the target compound into multiple pieces. So one group is methyl (CH_3), and the other group is phenyl.

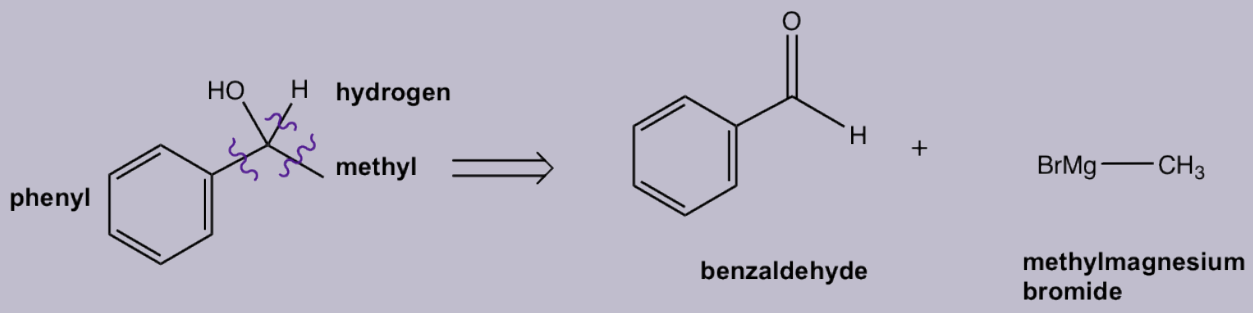


Step 3: Now we can decide the structure of the reactants. While there is no other restriction for the reactants for this question, there are two options available.

Option 1: Phenylmeganesium bromide and acetaldehyde



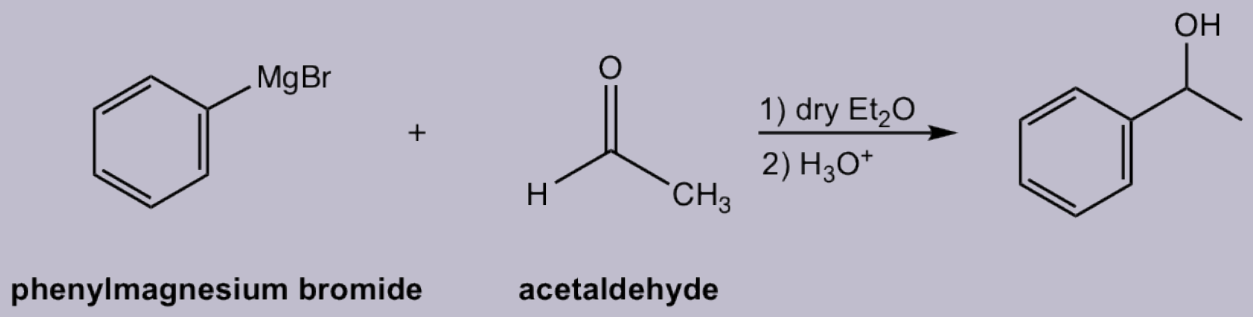
Option 2: Methylmeganesium bromide and benzaldehyde



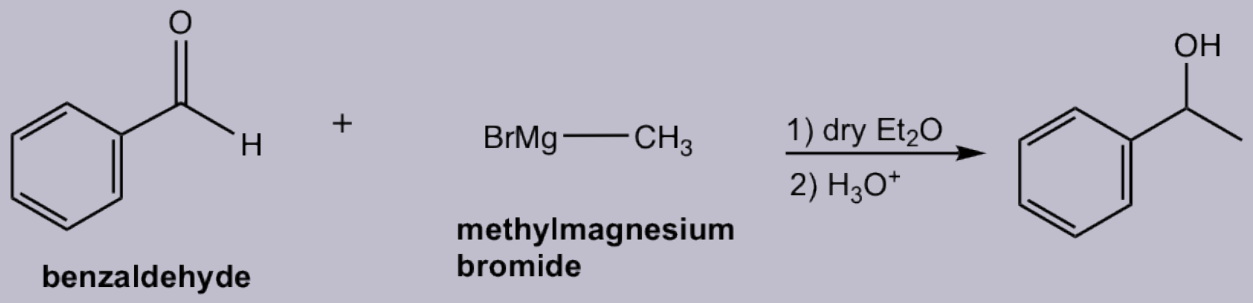
Note: Please double check that the number of carbons in the product **equals** the add-up of the number of carbons in both reactants, to make sure you did not miss out or use too many carbons.

Answer:

Synthesis method I:

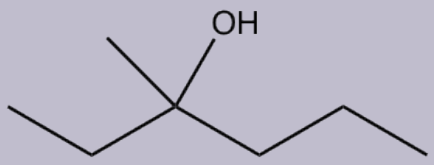


Synthesis method II:



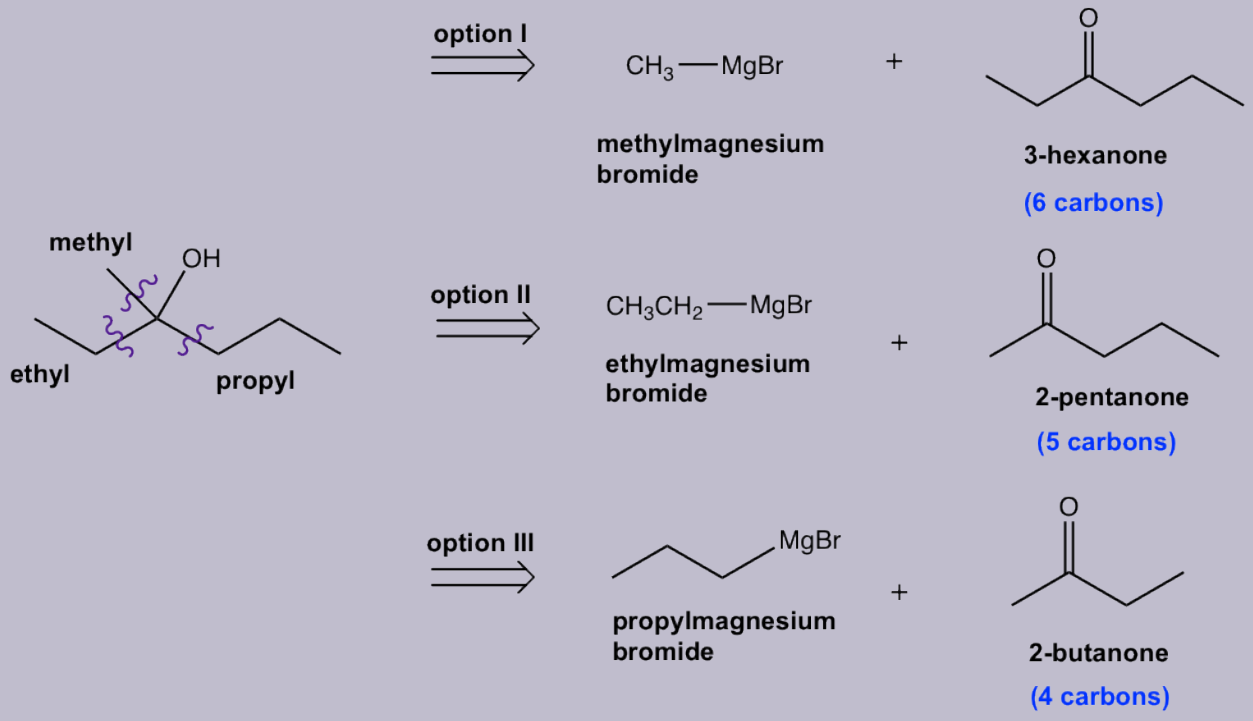
Example B:

Outline a synthesis of the following compound by using halides and carbonyl compounds of ***no more than four carbon atoms*** as organic starting materials. Other inorganic compounds and solvents can be used as necessary.



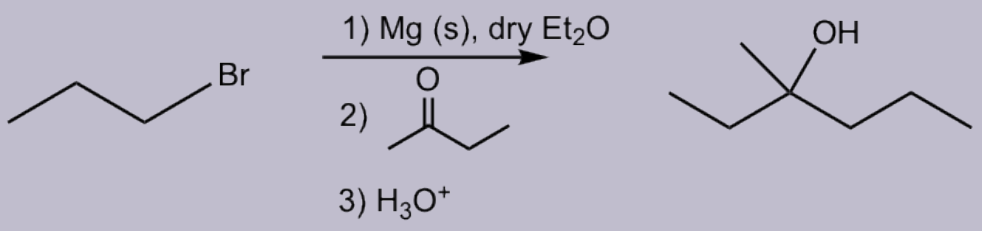
Analysis:

By applying the strategy we have learned, there are three options available for combinations of Grignard reagents and ketones for this question, as shown here. However, because of the extra requirement that all organic reagents should have ***no more than four carbons***, only option III works as the solution to this question.



Please note that such extra requirements are very common for synthesis design questions.

Answer:


Br
1) Mg (s), dry Et2O
2)
O
3) H3O+
OH

1.5 Williamson Ether Synthesis

Here we will only have discussions on Williamson ether synthesis, the most well-known and effective method for the synthesis of unsymmetrical ethers. The reaction goes through the S_N2 mechanism (refer to **section 7.3 in Book I**), with alkoxides (act as nucleophiles) reacting with substrates that bear a good leaving group.

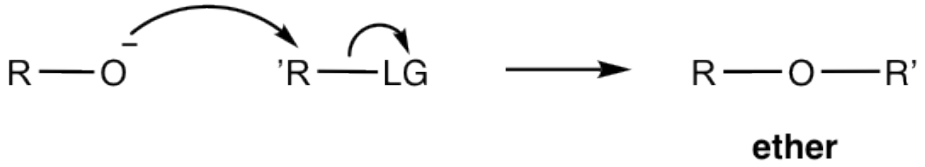


Fig. 1.5a Williamson Ether Synthesis (SN2 mechanism)

Because of the S_N2 nature of the reaction, primary or secondary substrates are typical for Williamson synthesis, with primary (and methyl) substrates giving the best results. Elimination occurs for tertiary substrates. Alkoxide can be produced by treating the alcohol with sodium or sodium hydride. An example of the synthesis of ethyl propyl ether from propanol and ethyl bromide is shown below.

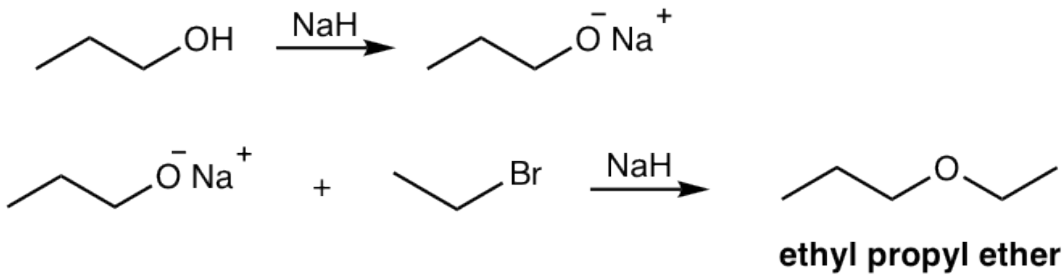
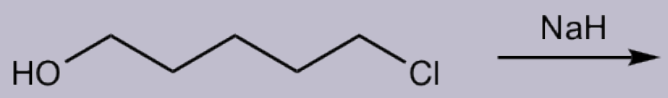


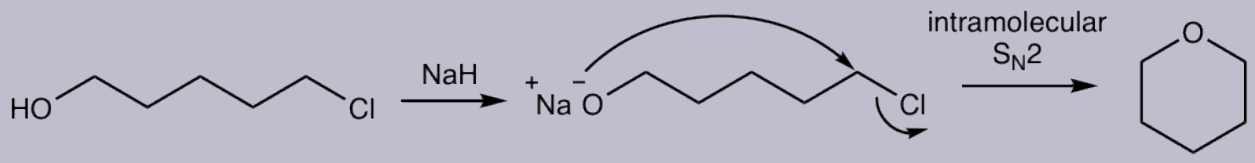
Fig. 1.5b Williamson Ether Synthesis Example of Ethyl Propyl Ether

Examples

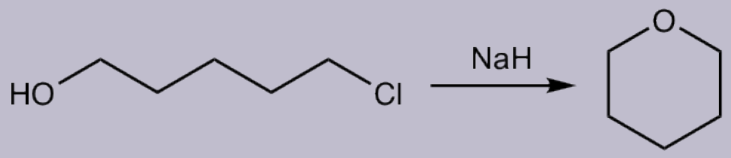
Show the product of the following reaction.



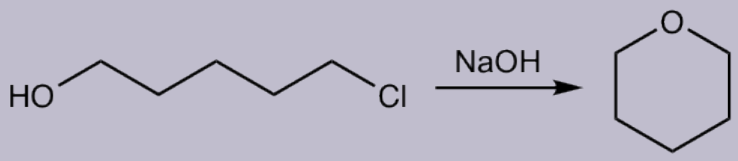
Analysis: Alkoxide is produced from the reaction of alcohol (OH group) with NaH, the alkoxide then reacts with chloride by ***intramolecular*** S_N2 mechanism to give the cyclic ether.



Answer:



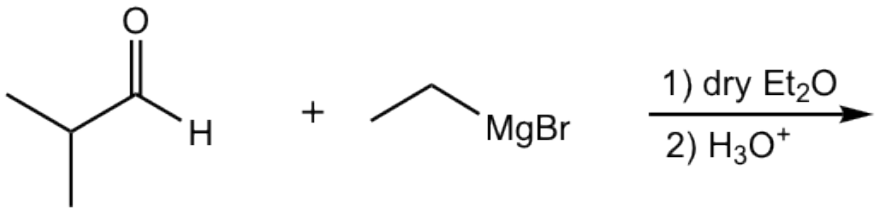
NaOH works for the above synthesis as well. Even the reaction between alcohol and NaOH does not favor the large equilibrium concentration of alkoxide, the fast intramolecular reaction of alkoxide with chloride helps to drive the equilibrium to the product side.



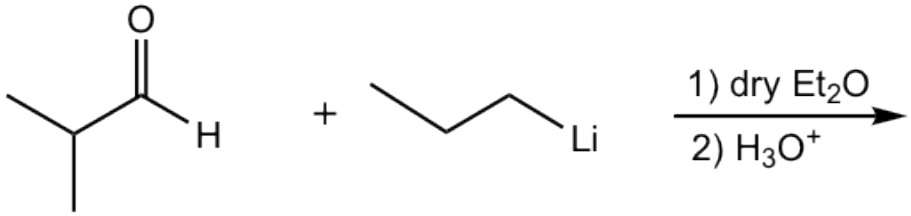
1.6 Practices

1. Show the product of the following reactions.

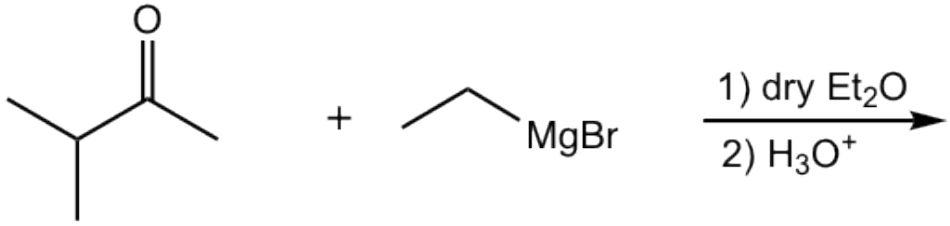
a.



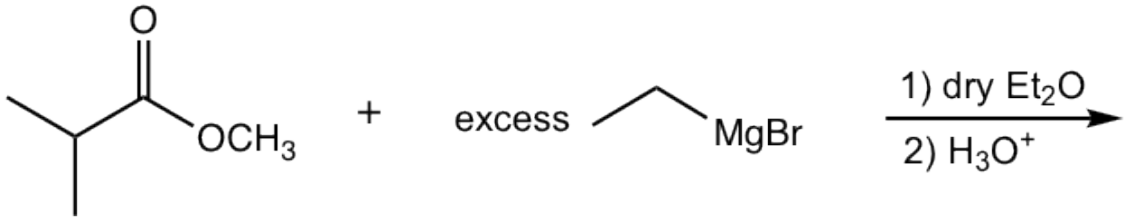
b.



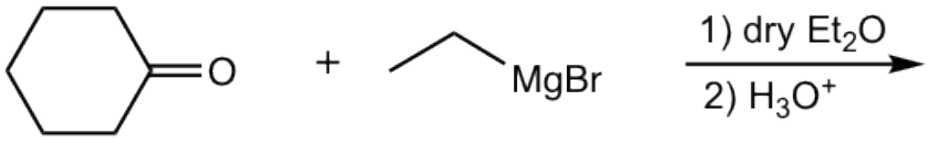
c.



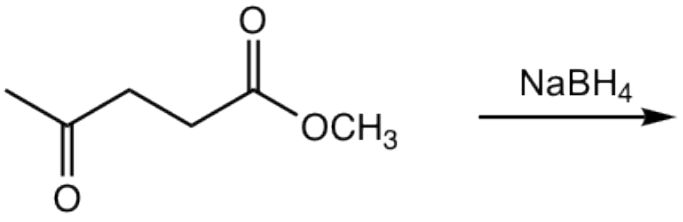
d.



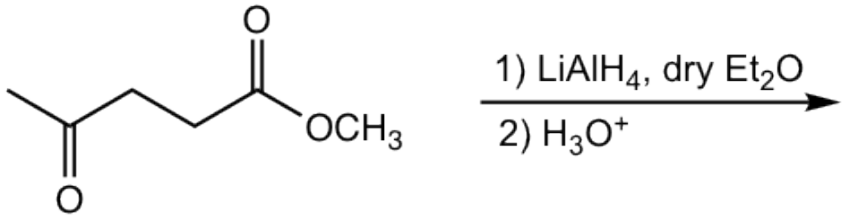
e.



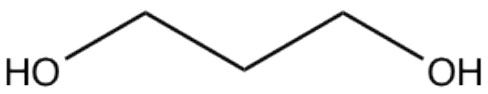
f.



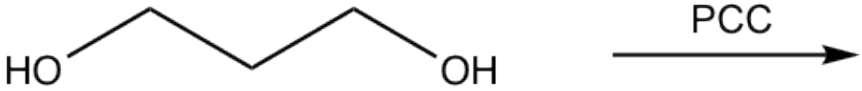
g.



h.

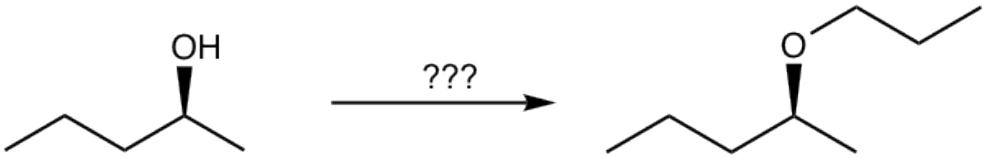


i.

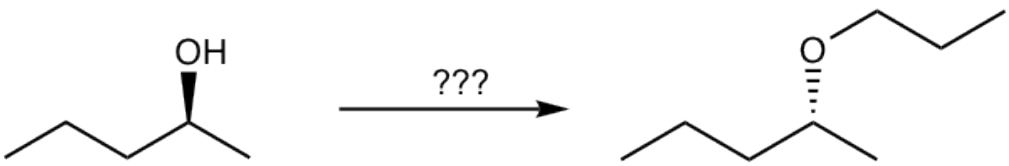


2. Show the detailed steps to synthesize the following ethers using Williamson synthesis. Other reagents and solvents can be used as necessary.

1)

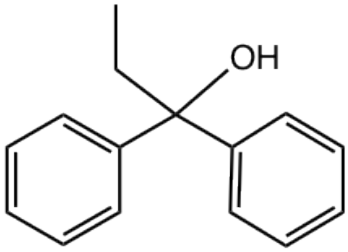


2)

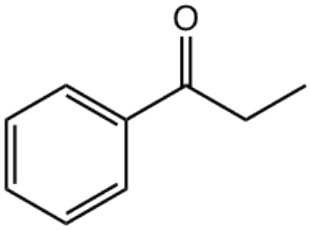


3. Propose the synthesis for each of the following compounds, based on the starting materials specified.

a. Start with methyl propanoate and other necessary chemicals/reagents.



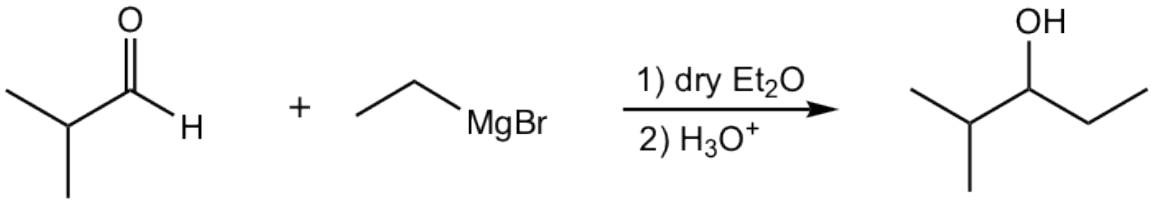
b. Start with phenylmagnesium bromide and other necessary chemicals/reagents.



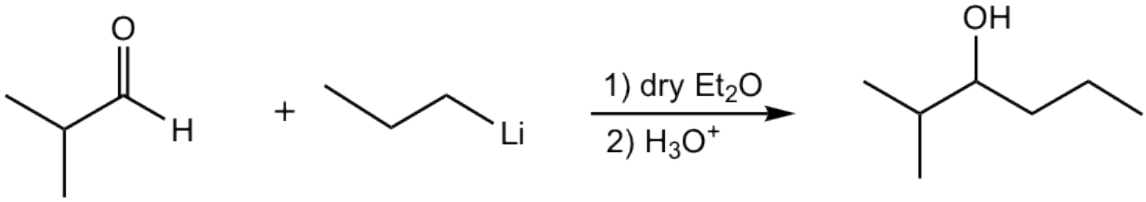
1.7 Practices Answers

1. Show the product of the following reactions.

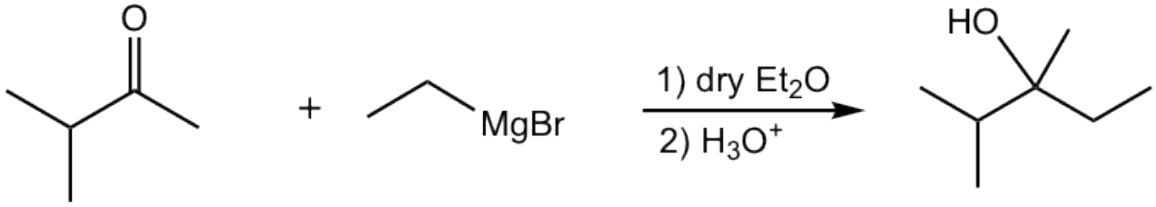
a.



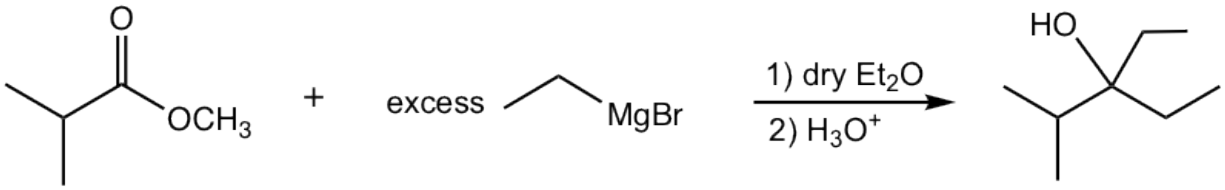
b.



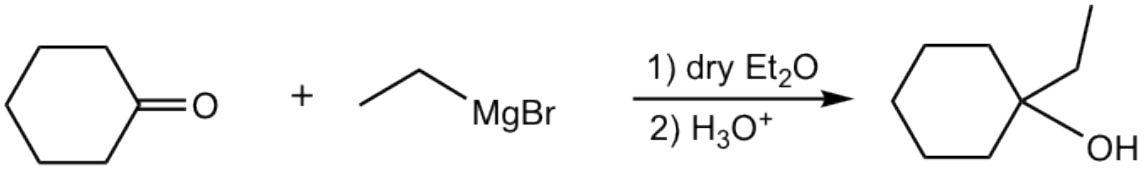
c.



d.



e.



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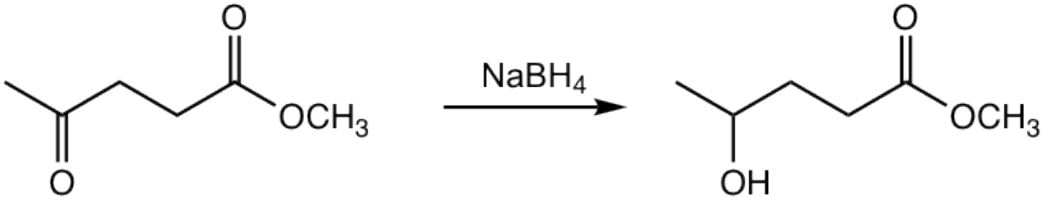
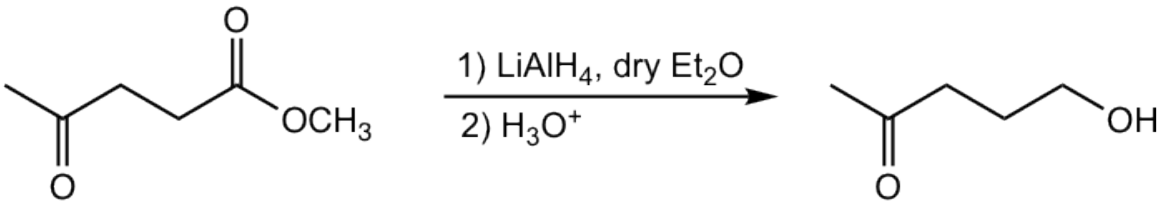
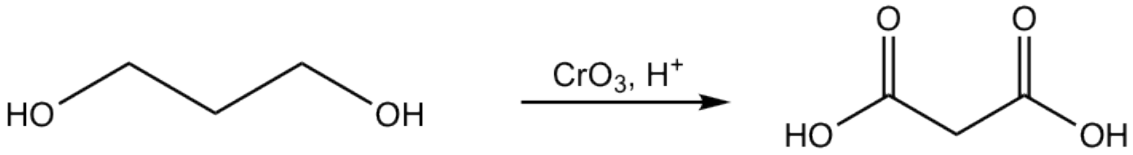


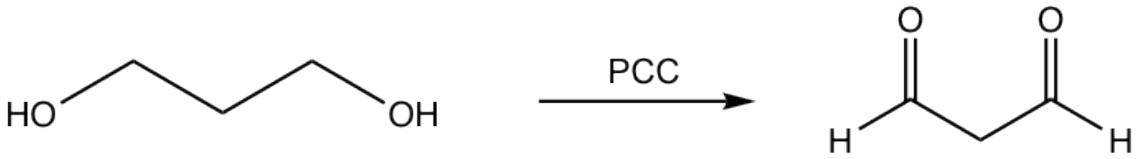
g.



h.



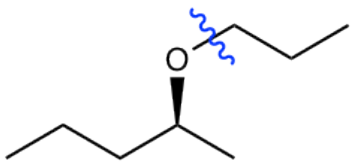
i.



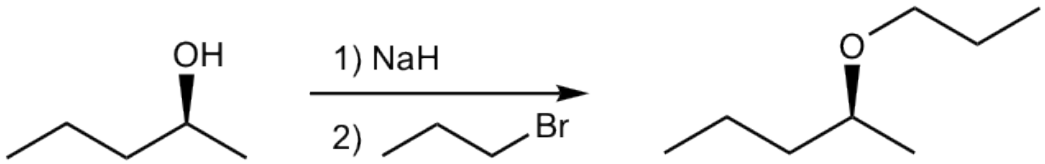
2. Show the detailed steps to synthesize the following ethers using Williamson synthesis. Other reagents and solvents can be used as necessary.

Tips for 1): To keep the configuration of the reactant retained in the product, the chirality center should not be involved in the reaction, therefore the reactant S-2-pentanol should be converted to the nucleophile, and reacts with halide. The bond-breaking position is shown below.

1)

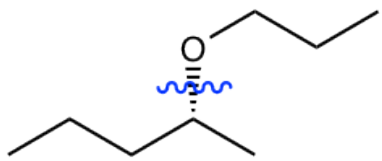


Answer for 1):

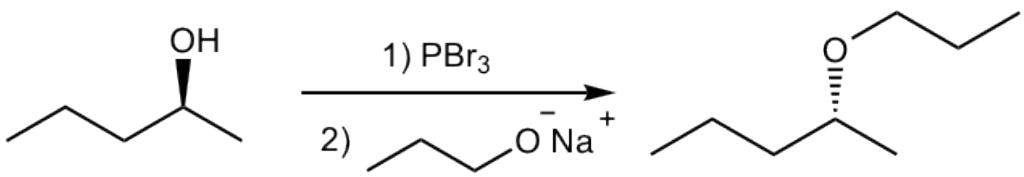


Tips for 2), to get the inversed configuration in the product, the SN2 reaction should occur on the chirality center, therefore the S-2-pentanol should be converted to a halide (LG), and react with another nucleophile. The bond-breaking position is shown below.

2)



Answer for 2):

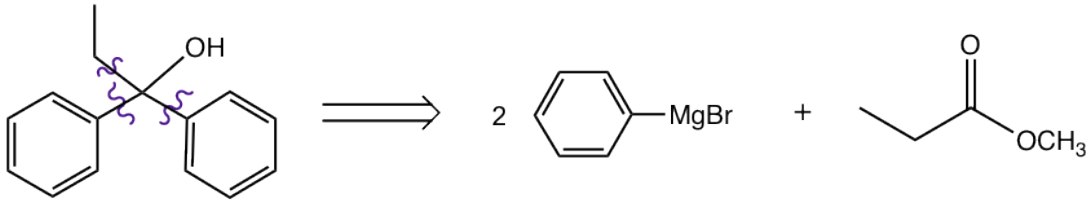


3. Propose the synthesis for each of the following compounds, based on the starting materials specified.

a. Start with methyl propanoate and other necessary chemicals/reagents.

Retrosynthesis analysis:

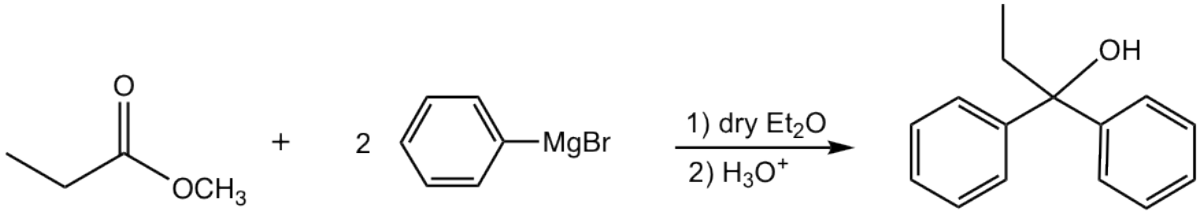
ethyl, from ester



two phenyl groups,

both from Grignard reagent

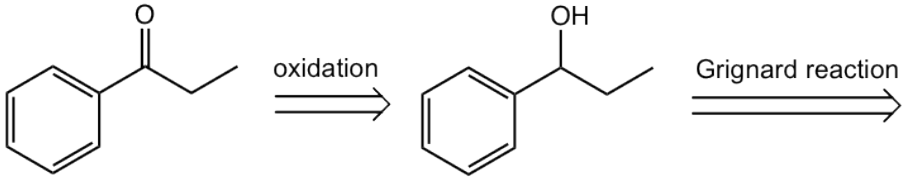
Answer:



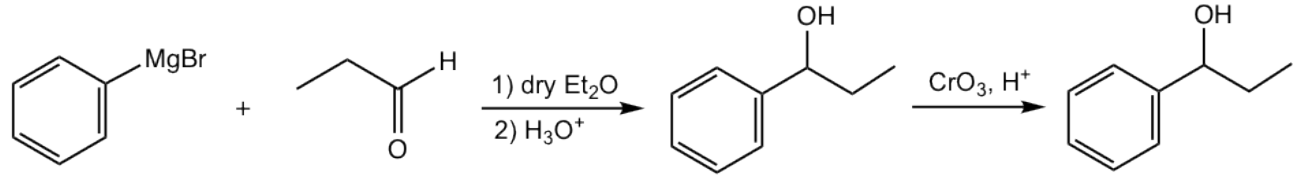
methyl propanoate

b. Start with phenylmagnesium bromide and other necessary chemicals/reagents.

Retrosynthesis analysis:



Answer:



phenylmagnesium bromide

propanal

CHAPTER 2: ALDEHYDES AND KETONES

2.1 Structures, Properties and Naming of Aldehydes and Ketones

For alcohol preparations, we have had some discussions about the reactions of aldehydes and ketones in **section 1.4 of Chapter 1**. Here we will get more insights into the the chemistry properties of aldehydes and ketones, which are the foundations of other reactions will be covered in this and the following chapters.

Both aldehydes and ketones contain the carbonyl (C=O) group, while the aldehyde must have at least one hydrogen atom bond with the carbonyl carbon, and ketone must have two alkyl (aryl) groups that could be either same or different, as shown in Fig. 2.1a.

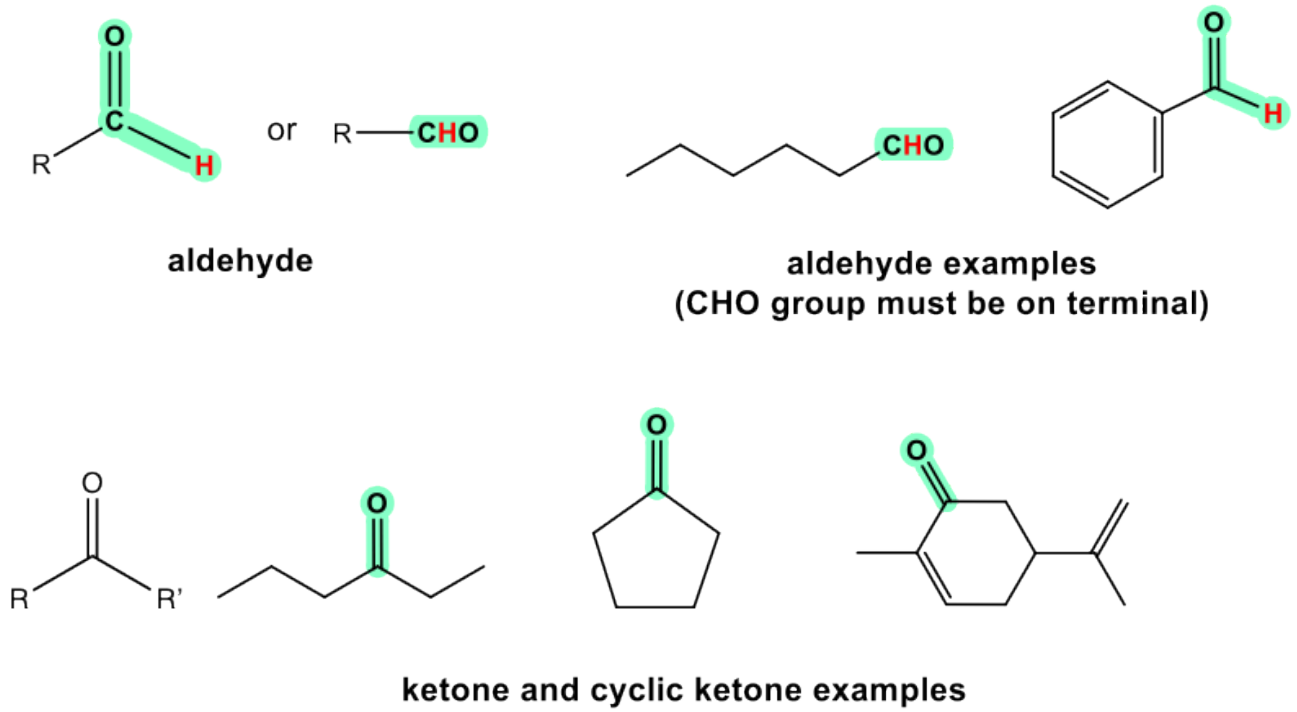


Fig. 2.1a Structures and Examples of Aldehydes and Ketones

Because of the polarity of the C=O bond, the carbonyl group is polar, and so are the aldehyde and ketone molecules. Dipole-dipole force is the major intermolecular force applied to aldehydes and ketones, as such the boiling points of aldehydes or ketones are higher than that of the hydrocarbon with a similar molar mass. The polarity however decreases with the carbon chain increase, since the polarity of the C=O bond is overridden by the non-polar hydrocarbon chain.

Even though hydrogen bonding does not apply between aldehyde and ketone molecules, they are good hydrogen bond acceptors. The two electron pairs on the oxygen atom of the carbonyl group are ready to form H-bonds with water molecules. That explains the good solubility of smaller size aldehydes and ketones.

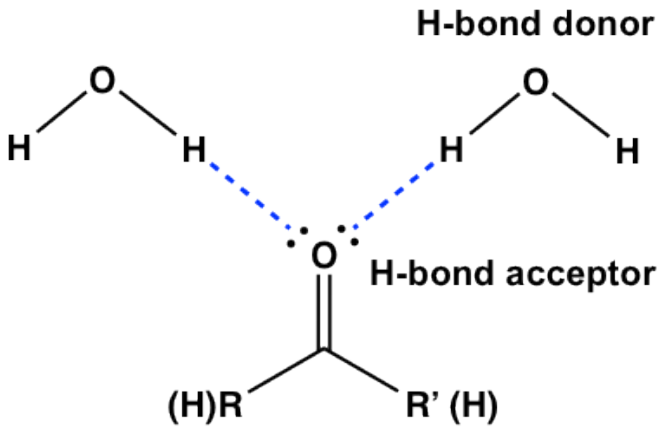


Fig. 2.1b Aldehydes or Ketones are hydrogen bond acceptors

The physical properties of some common aldehydes and ketones are listed in **Table 2.1**.

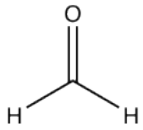
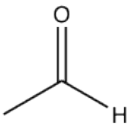
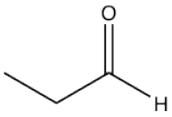
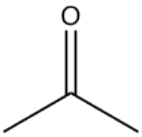
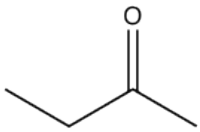
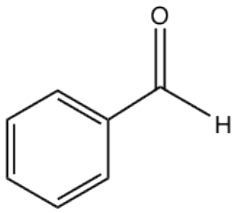
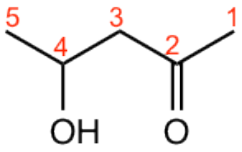
Name	Structure	Boiling Point (°C)	Solubility in water
Formaldehyde		-21	infinite
Acetaldehyde		21	infinite
Propanal		49	very soluble
Acetone		56	infinite
Butanone		80	very soluble
Benzaldehyde		178	slightly soluble

Table 2.1 Physical properties of some common aldehydes and ketones

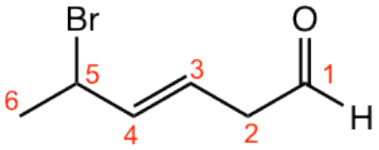
Simple aldehydes and ketones can be named by following the IUPAC rules we learned before (**section 2.4 of Book I**), with a couple of highlights here:

- Change the ending of the parent alkane/alkene/alkyne to the ***al*** for aldehyde, and ***one*** for ketone;
- The suffix **carbaldehyde** is added when the -CHO group is attached to a ring.

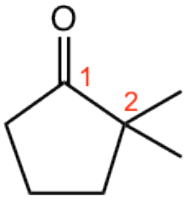
Several examples are given here to illustrate the IUPAC naming of aldehydes and ketones.



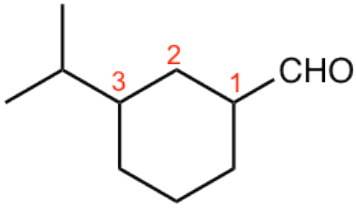
4-hydroxy-2-pentanone



***trans*-5-bromo-3-hexenal**



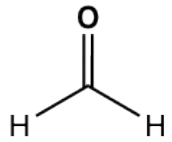
2,2-dimethylcyclopentanone



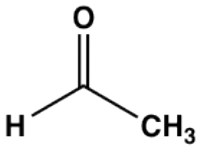
3-isopropylcyclohexanecarbaldehyde

Fig. 2.1c IUPAC naming of some aldehydes and ketones

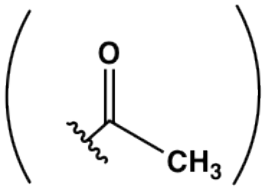
The common names have been adopted broadly (in this book as well) for following aldehydes and ketones.



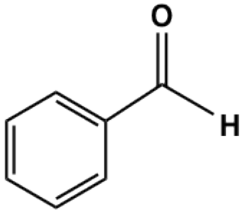
formaldehyde



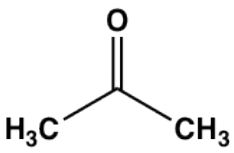
acetaldehyde



acetyl group (Ac)



benzaldehyde



acetone

Fig. 2.1d Common names of some aldehydes and ketones

2.2 Preparations of Aldehydes and Ketones

In the early chapter and Book I, we have learned several reactions that provide good methods for the preparation of aldehydes and/or ketones, let's have a review here.

Chapter 1 Review

Oxidation of 1° or 2° Alcohols (1.2.5)

Pyridinium chlorochromate (PCC) is the proper oxidizing reagent to oxidize 1° alcohol to aldehyde, and oxidize 2° alcohol to ketone.

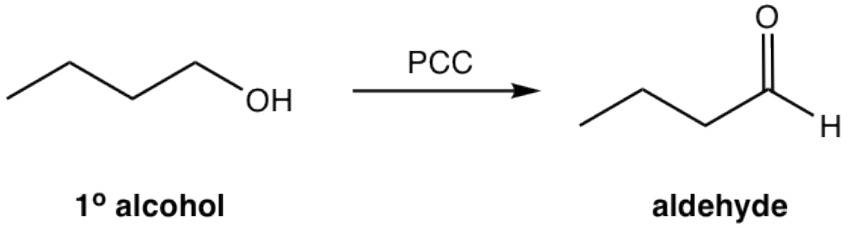


Fig. 2.2a Oxidation of primary alcohol by PCC

Ozonolysis of an Alkene (10.7.2 in Book I)

Ozonolysis reaction is the oxidative cleavage of the C=C double bond in the alkene, that produces aldehyde and/or ketone as products. It is a two-step process in which alkene reacts with ozone at a very low temperature (-78 °C) first, then treated with dimethyl sulfide, $(CH_3)_2S$, (or Zn/CH_3COOH) to give the products. A couple of examples are shown here.

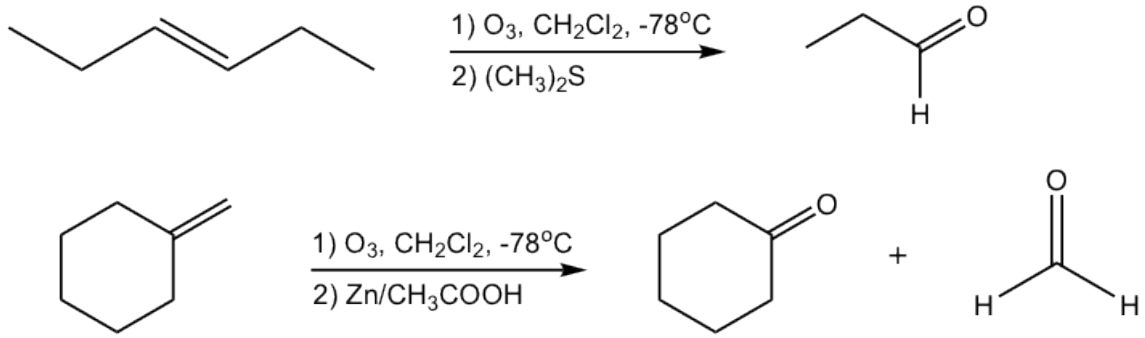


Fig. 2.2b Examples of Ozonolysis of alkenes

Hydration of an Alkyne (10.8 in Book I)

Starting from terminal alkyne, aldehyde can be prepared by hydroboration-oxidation, and methyl ketone can be prepared by hydration with Hg^{2+} as a catalyst.

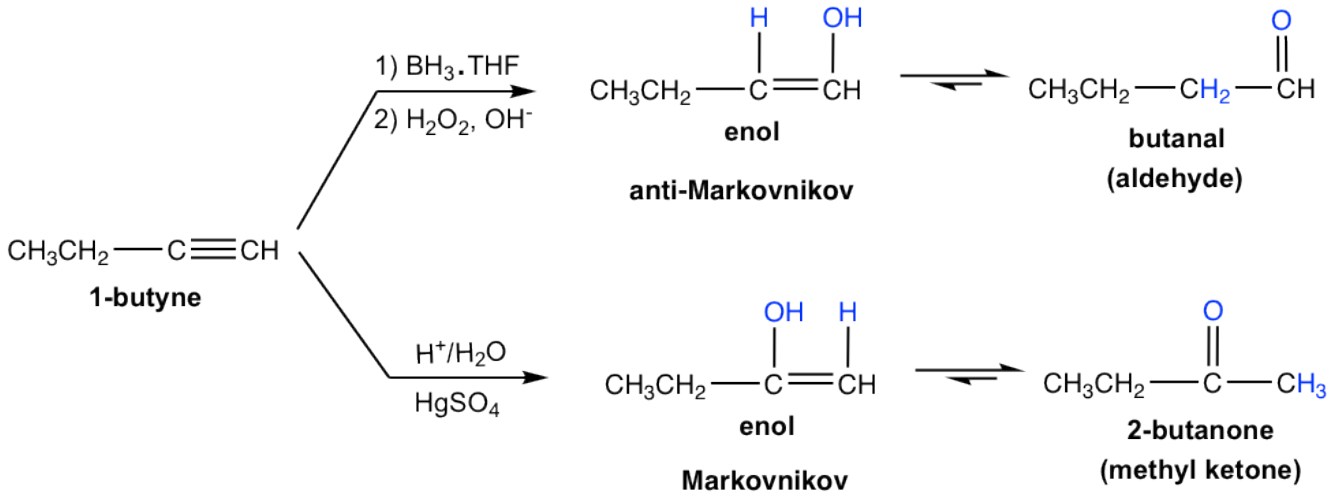


Fig. 2.2c Preparation of aldehyde or ketone from terminal alkynes

For internal alkyne, hydration with Hg^{2+} as a catalyst generates ketone as a product. For synthesis purposes, this method works best with ***symmetric*** internal alkyne that gives only one ketone product.

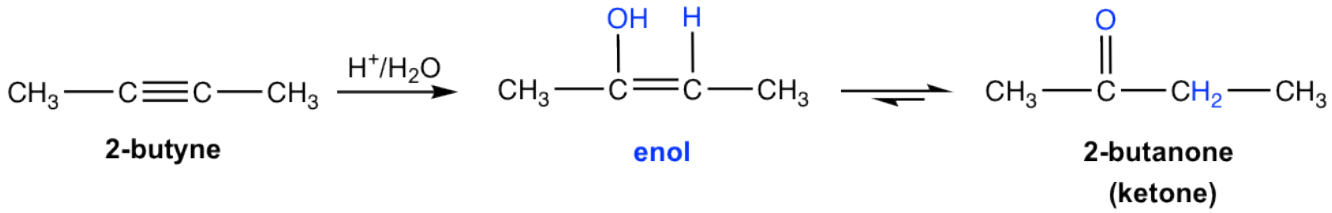


Fig. 2.2d Preparation of ketone from symmetric internal alkynes

Friedel-Crafts Acylation

Another important reaction that gives ketone as a product is Friedel-Crafts acylation, a type of Electrophilic Aromatic Substitution (EAS) reaction. We will have thorough discussions on EAS and Friedel-Crafts reaction in Chapters 4 and 5. An example is shown here for general purposes.

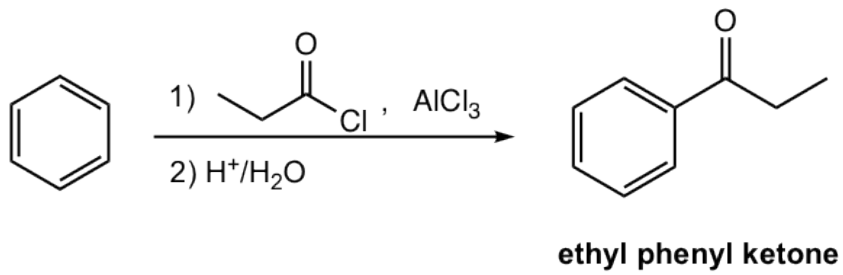


Fig. 2.2e Example of ketone preparation by Friedel-Crafts Acylation

2.3 Reactivities of Aldehydes and Ketones

In section **1.5.1**, we have had a general discussion about the structure features and reactivities of the carbonyl group. More discussions will be needed here to understand the reaction diversities of this functional group.

2.3.1 Regions of Reactivity in Aldehydes and Ketones

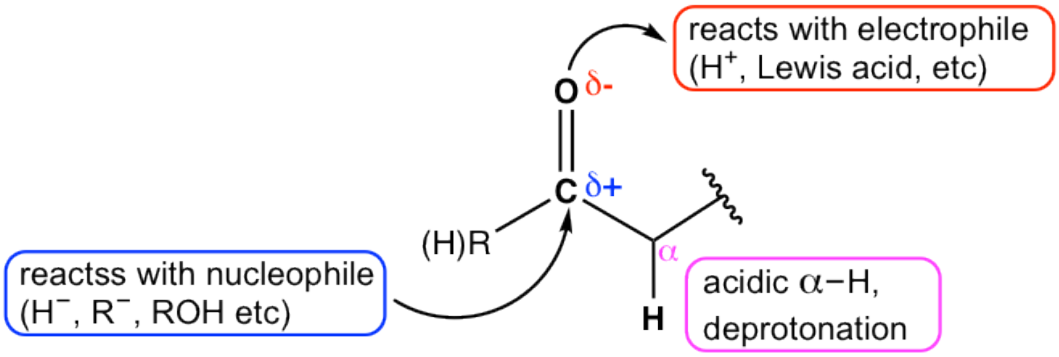


Fig. 2.3a Reactivity centers in aldehyde and ketone

For carbonyl compounds, there are **three** reactivity centers as highlighted in Fig. 2.3a.

1. **The carbonyl carbon**. Because of the polarity of the C=O bond, the carbon atom bears a partial *positive* charge, therefore it is electron-poor, and a great target for the attack by an electron-rich nucleophilic group. The reactions of metal hydrides (section **1.4.2**) and organometallic reagents (for example Grignard reagent in section **1.4.4**) with aldehydes and ketones are examples of this reactivity center. More reactions with a diversity of nucleophiles will be discussed in upcoming sections.
2. **The oxygen atom**. For the same reason of C=O bond polarity, the oxygen atom bears a partial *negative* charge. Being an electron-rich spot, the oxygen atom is ready to react with other electrophiles, such as H^+, or Lewis acid. Protonation is a common reaction for carbonyl oxygen when acid is present.
3. The position that is adjacent to the carbonyl carbon, is called the **α-position**. Recall that the hydrogen atom at this position has a pK_a of about 16~20 (**section 3.3 in Book I**). Deprotonation with a strong base readily occurs for **α-hydrogen**, and then triggers a series of interesting and important reactions. This will be the topic in Chapter 6.

The first two reactivity centers (carbon and oxygen atoms) will be the focus of this chapter. Because of the reactivity mentioned above, the most common and characteristic reaction of aldehyde and ketone is the addition of the carbonyl group with nucleophile, that is **nucleophilic addition**, the reactions we have learned in section **1.4.2** and **1.4.4** fit in this category. The general equation of nucleophilic addition for aldehydes and ketones is shown below.

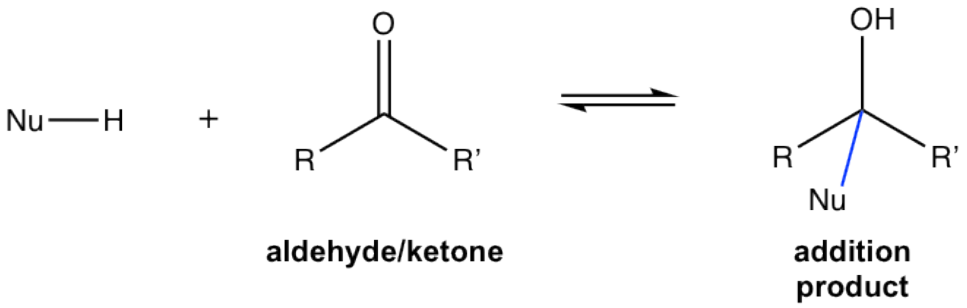


Fig. 2.3b General equation of nucleophilic addition. (NuH is used here for general purposes, the nucleophile does not have to be neutral)

Depending on the strength of different nucleophiles, the detailed mechanism might be different, and there are generally ***two types of mechanisms*** for addition with strong nucleophiles (Fig. 2.3c) or weak nucleophiles (Fig. 2.3d) respectively. The mechanisms shown below are just for general purposes to help you gain the big picture of **nucleophilic addition**, the detailed steps and structure of products for different reactions still need specific attention.

Mechanism I — Nucleophilic addition with strong negatively charged nucleophile (Nu^-):

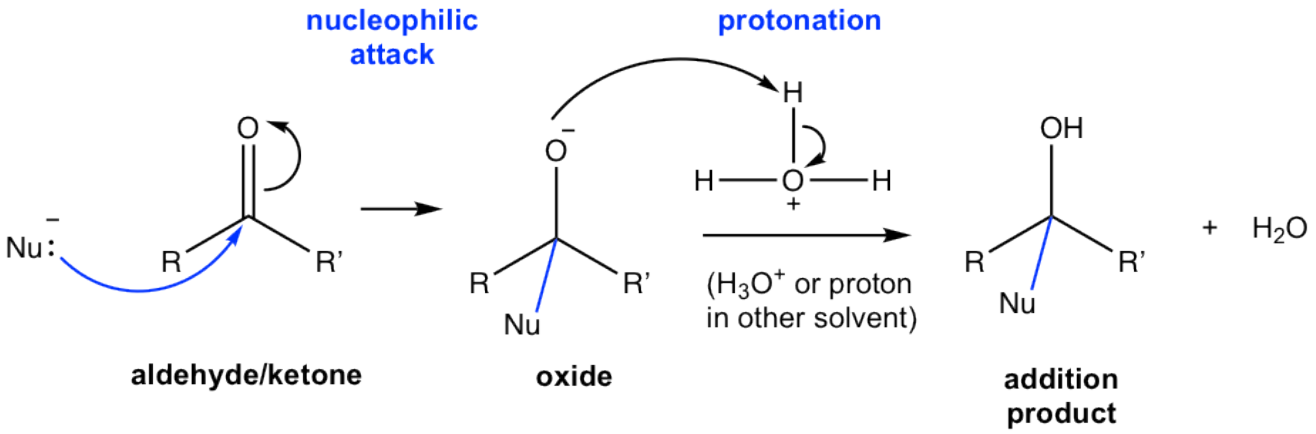


Fig. 2.3c Nucleophilic addition with strong nucleophile

Because of the strong nucleophilicity of such nucleophiles, the nucleophilic attack occurs directly on carbonyl carbon in the first step, and a new bond is formed between the carbon and the nucleophile. A tetrahedral intermediate with full negative charge on oxygen (an oxide) is produced in this step. Such oxide anion, as a strong base, is susceptible to protonation with the solvent to give a neutral addition product. The overall addition involves two steps: **nucleophilic attack, followed by protonation.** The addition reactions of hydride (H^-), organolithium reagent (RLi), and Grignard reagents (RMgX) (**1.4.2 and 1.4.4**) are typical examples of this category.

Mechanism II — Nucleophilic addition with weak nucleophile (NuH) and acid catalyst present:

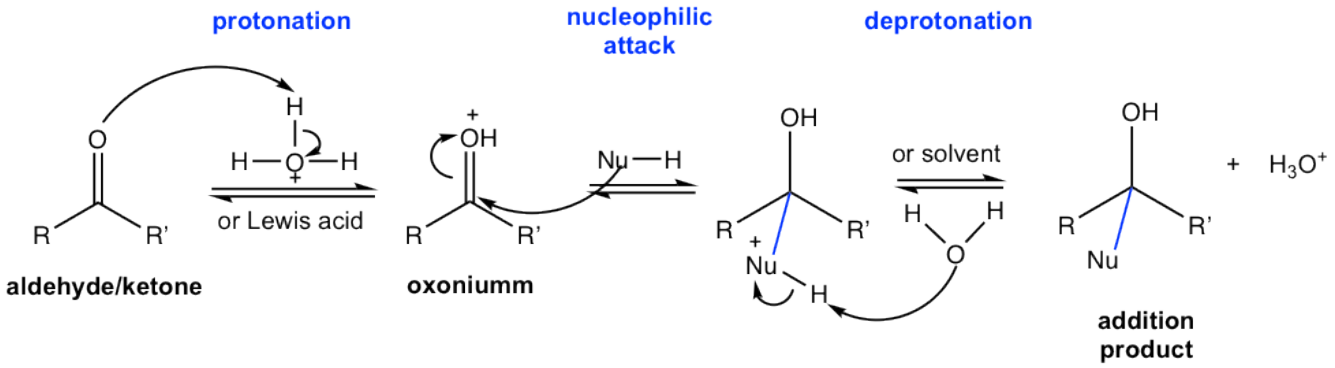


Fig. 2.3d Nucleophilic addition with weak nucleophile

The carbonyl carbon, which bears only a partial positive charge, is not a strong electrophile. Therefore the ability of weaker nucleophiles, such as ROH and water, are not strong enough to do the attack directly. However, with catalytic acid present, the carbonyl group undergoes protonation first, and the protonated version of the carbonyl group, oxonium, exhibits stronger electrophilicity that is prone to react with weak nucleophiles. The overall addition therefore involves three steps: **protonation, nucleophilic attack, and deprotonation**.

Another point is that many nucleophilic additions to the carbonyl group are reversible. The structure and nature of reactants determine the overall results, or the position of the equilibrium.

2.3.2 Reactivity Difference between Aldehyde and Ketone

The structural difference between aldehyde and ketone is that there must be at least one hydrogen atom in the aldehyde, while ketone has two R groups. For steric hindrance, the larger R group makes it more crowded around the carbonyl carbon, and slows down the attack of the nucleophile. Furthermore, the e-donating effect of the R groups in ketone helps to stabilize the partial positive charge on the carbonyl carbon, and makes ketone to be less reactive towards nucleophilic attack.

As a result, **generally, aldehydes are more reactive than ketones for nucleophilic addition.**

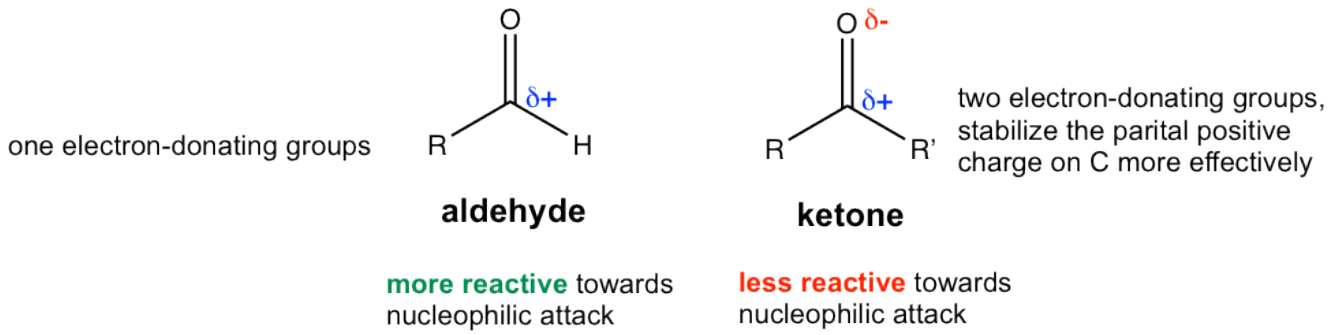

one electron-donating groups
aldehyde
ketone
two electron-donating groups, stabilize the parital positive charge on C more effectively
more reactive towards nucleophilic attack
less reactive towards nucleophilic attack

Fig. 2.3e Reactivity difference between aldehyde and ketone

In upcoming sections (**2.4 ~ 2.7**), we will learn more specific reactions between aldehydes/ketones with different nucleophiles.

2.4 Addition of Water to Aldehydes and Ketones

Aldehydes undergo the addition of water under either acidic or basic conditions. The addition of water can also be called hydration, that produces hydrate of aldehyde or ketone.

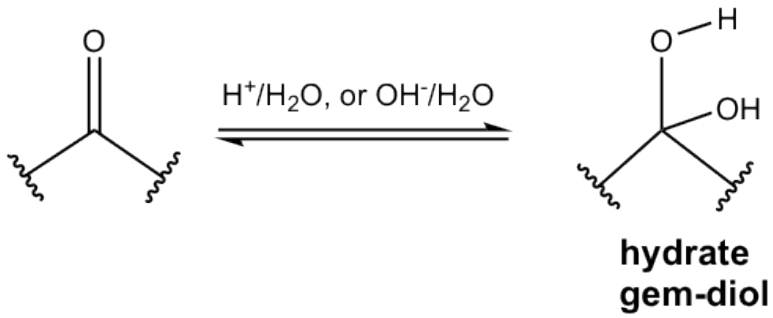


Fig. 2.4a General equation for hydration of aldehydes and ketones

In the hydration product, a water molecule (H-OH) is added to the C=O bond, specifically the OH group is connected to the carbon atom, and the H bonds to the oxygen atom. The product, therefore, has two OH groups on two adjacent carbons, such functional group is also called the geminal diol (*gem*-diol).

The mechanism for hydration reaction in basic conditions fits in **mechanism I** (Fig. 2.3c), and that in acidic conditions is a good example of **mechanism II** (Fig. 2.3d). The detailed mechanisms for hydration are shown below.

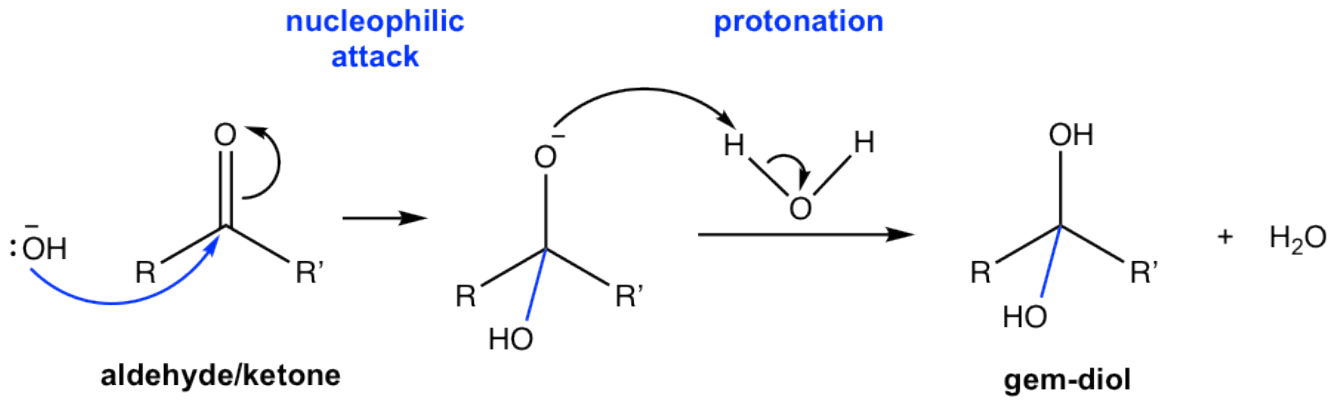


Fig. 2.4b Mechanism for hydration of aldehyde/ketone in basic condition

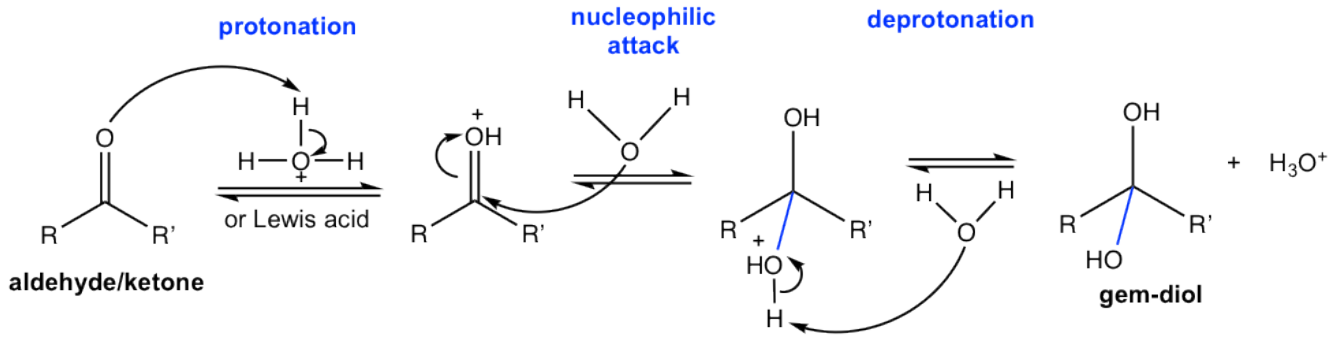


Fig. 2.4c Mechanism for hydration of aldehyde/ketone in acidic condition

In most cases, the resulting hydrate (*gem*-diol) is unstable and cannot be isolated. The effort of heating to isolate hydrate results in evaporation of water, and pushes the equilibrium to the carbonyl compound side, and the hydrate is converted back to carbonyl compound.

Because of the relatively low reactivity of ketone towards nucleophiles, the equilibrium for the hydrate of ketone is unfavorable. On the other side, the hydrate predominates the equilibrium for some aldehydes (Fig. 2.4d). One example is that the aqueous solution of formaldehyde (formalin) contains primarily the hydrate $CH_2(OH)_2$. Also, the presence of strong electron-withdrawing groups destabilizes the carbonyl group and tends to form stable *gem*-diols. The equilibrium of chloral hydrate provides a typical example of such a case (in Fig. 2.4d).

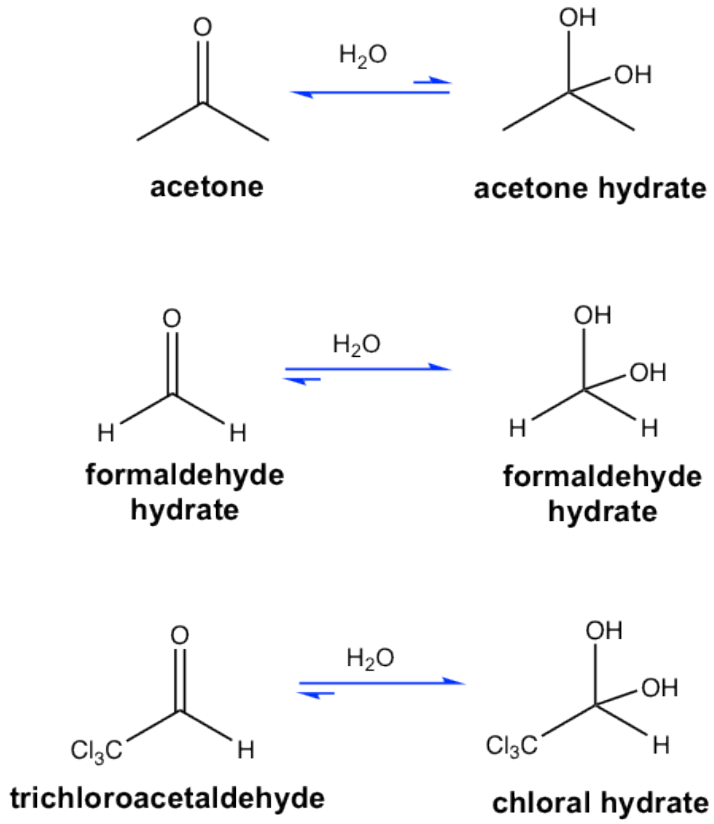


Fig. 2.4d Equilibrium of hydrates for different aldehydes or ketones

2.5 Addition of Alcohols to Aldehydes and Ketones

The carbonyl group in aldehyde and ketone also reacts with alcohol, another nucleophile, in the presence of an ***acid catalyst***. The initial nucleophilic addition gives **hemiacetal** as a product, and the reaction continues with another equivalent of alcohol to form an **acetal**.

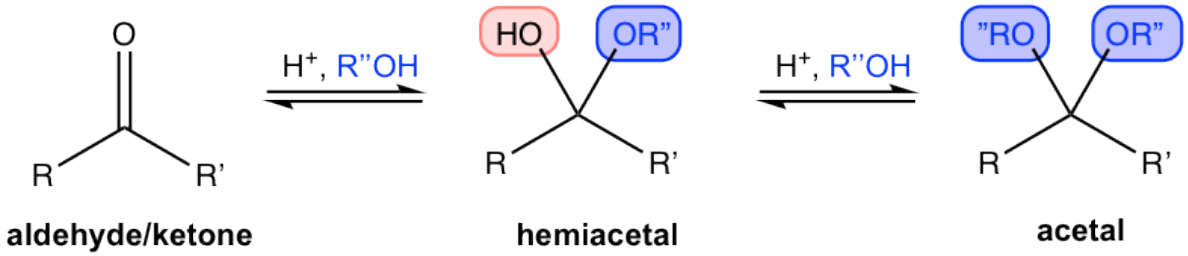


Fig. 2.5a General reaction of alcohol with aldehyde or ketone

Formation of Hemiacetals

The mechanism for hemiacetal formation fits in the general **Mechanism II** (Fig. 2.3d) pretty well, which involves ***protonation***, ***nucleophilic attack*** by alcohol, and ***deprotonation***.

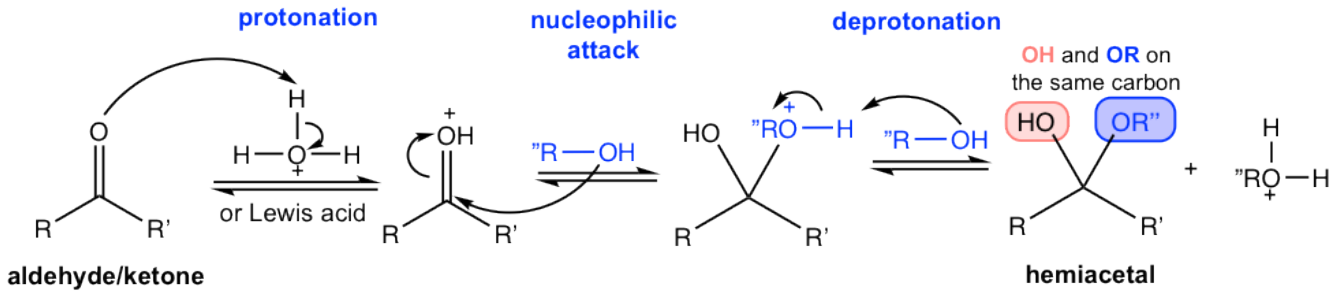


Fig. 2.5b Mechanism for the formation of hemiacetal

Hemiacetals are usually not stable enough to be isolated as the product. The special case is cyclic hemiacetals with 5- or 6-membered rings that can be isolated because of the stability of the ring.

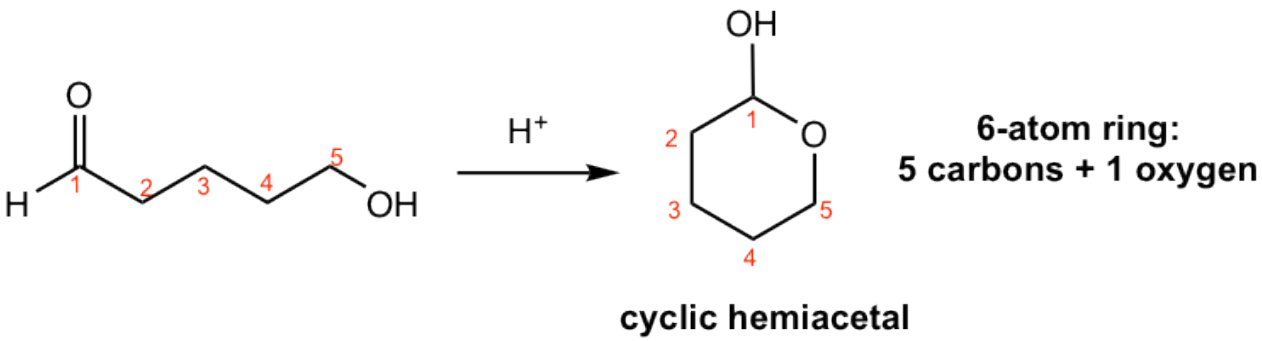


Fig. 2.5c Intramolecular reaction for cyclic hemiacetal

One typical example of cyclic hemiacetal is sugar. For example, the majority of glucose molecules adopt the cyclic hemiacetal structure in a solution of glucose (Chapter 9).

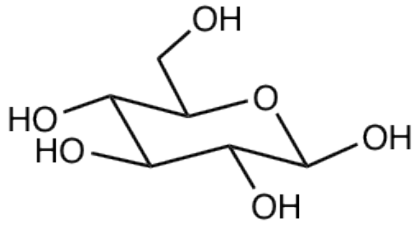


Fig. 2.5d D-(+)-Glucose in cyclic hemiacetal format

Formation of Acetals

The mechanism from hemiacetal to the formation of acetal is shown in Fig. 2.5e.

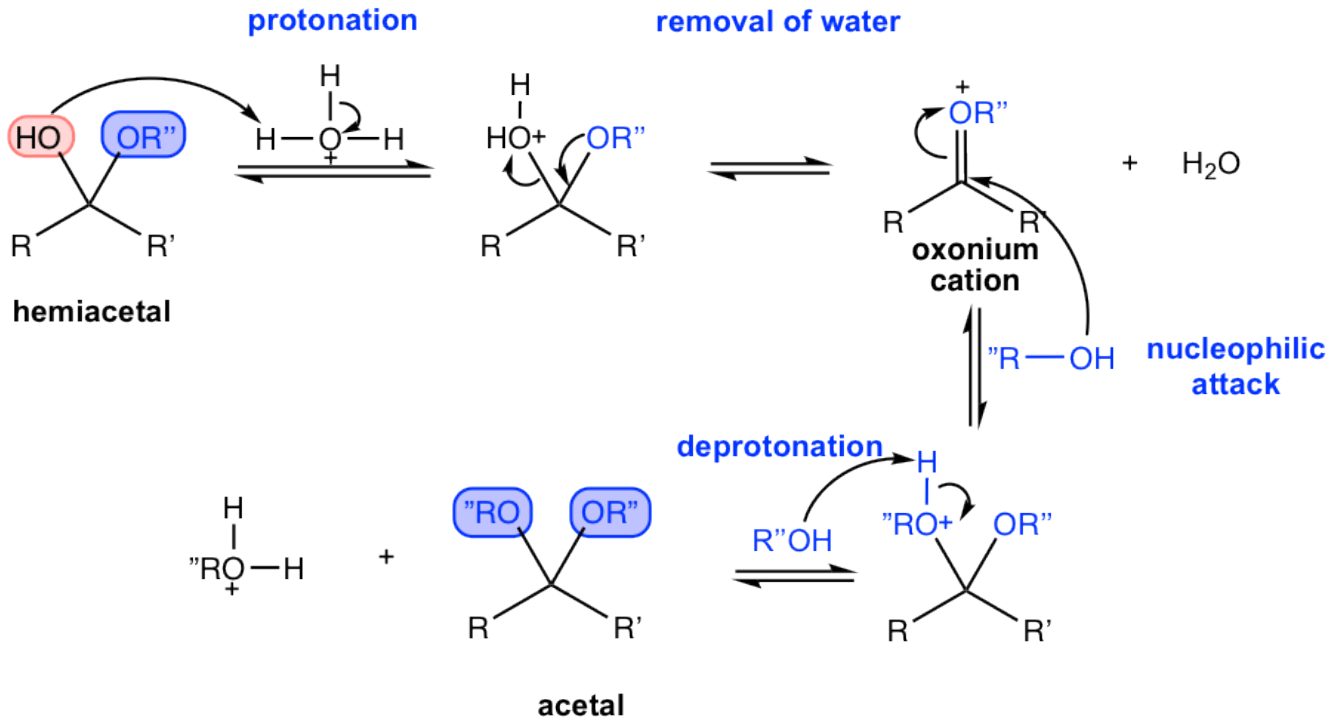


Fig. 2.5e Mechanism from hemiacetal to acetal

Starting from hemiacetal, protonation occurs again on the OH group. The reason for this protonation is to transfer OH (in hemiacetal) to H_2O, or a poor leaving group to a good leaving group, so water could be removed. After the removal of water, another alcohol does the nucleophilic attack on the oxonium cation intermediate, which leads to the product acetal with another deprotonation.

Since all the steps for the formation of hemiacetals and acetals are reversible, several practical tips are usually applied in the reaction to achieve a high yield of the product. First, a large access of alcohol is usually added to the reaction because of the availability of alcohol. Secondly, water, the side product of the reaction, is removed from the reaction process. Both measures help the equilibrium to strongly favor the product side and ensure a good yield of the acetal.

Notes for the mechanism of hemiacetal and acetal formation:

The mechanism for the formation of hemiacetal and acetal involves multiple steps, it might feel overwhelmed when you learn that the first time. They are very important mechanisms though, and being able to draw the full mechanism (including the mechanism for the reverse process, i.e., hydrolysis of acetal, in the following section) is part of the learning objective for the course at this level. There are a few tips to help you understand and memorize the mechanism more easily.

- **Nucleophilic addition** is the keyword, and alcohol (ROH) works as the nucleophile to attack the

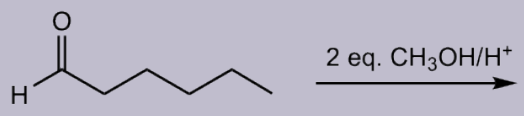
carbonyl carbon in these mechanisms.

- Since alcohol is a weaker nucleophile, protonation occurs first in the presence of acid and the protonated carbonyl is more reactive with alcohol nucleophile.
- Another protonation step is involved from hemiacetal to acetal, but for different purposes. In this part of the mechanism, protonation helps to transfer OH (the poor leaving group in hemiacetal) to a good leaving group H_2O, and then water could be removed.
- The mechanism is always product-oriented. In which way it makes sense to achieve the product, the reaction proceeds that way likely.

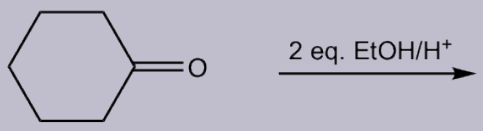
Examples:

Show the product of the following reactions.

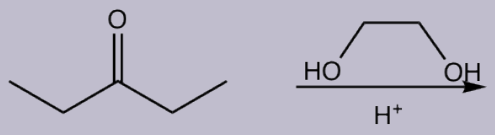
1)



2)

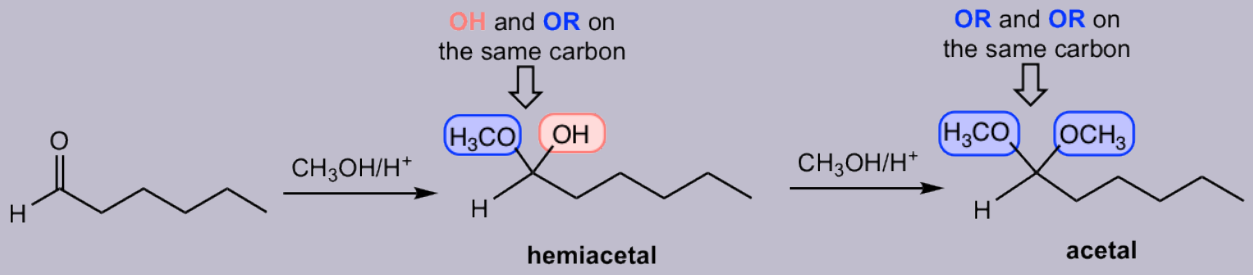


3)

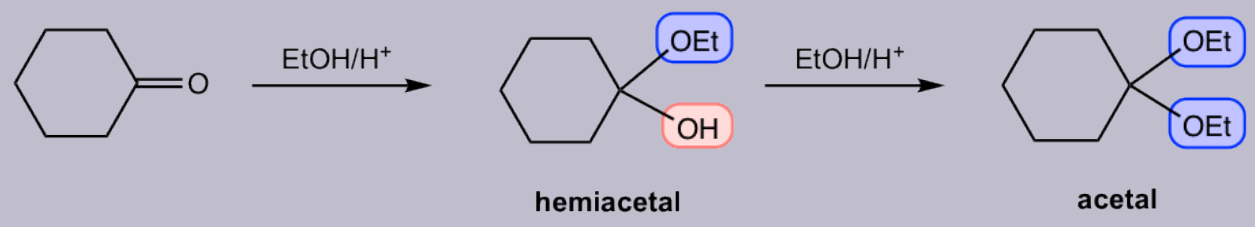


Answers:

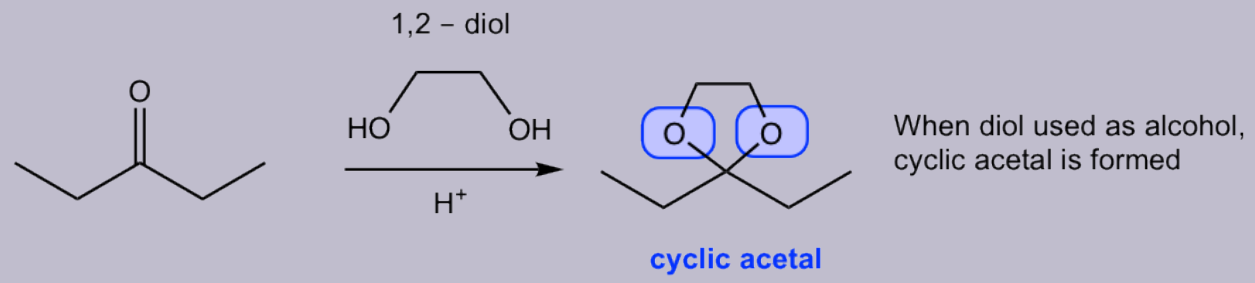
1)



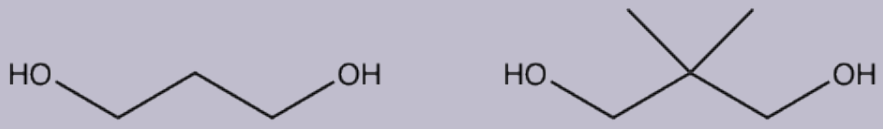
2)



3)



As shown in the last example #3), cyclic acetal is formed when diol is used as alcohol. Other diols that could be used for cyclic acetals include 1,3-propanediol, 2,2-dimethyl-1,3-propanediol.



Notes regarding the structures of hemiacetals and acetals:

Being able to recognize the structures of hemiacetals and acetals is critical. Both functional groups are brand new to us, and both have unique structure features. The key structure of **hemiacetal is that one OH and one OR are both attached to the same carbon atom**, which is kind of a "mixed structure of alcohol and ether". For acetal, on the other hand, the key feature is that two OR groups share the same carbon. As shown in the above examples, the groups are highlighted in different colors to make it easier for you to recognize and compare. It is more challenging to recognize when the ring is involved in the functional group, see practice question #1 at the end of the chapter.

Hydrolysis of Acetal

In the preparation of acetal, as it was mentioned earlier, water should be removed from the reaction system to favor the equilibrium of the product side. On the other side, if acetal is placed in excess water with acid present, acetal undergoes **hydrolysis** and goes back to aldehyde or ketone.

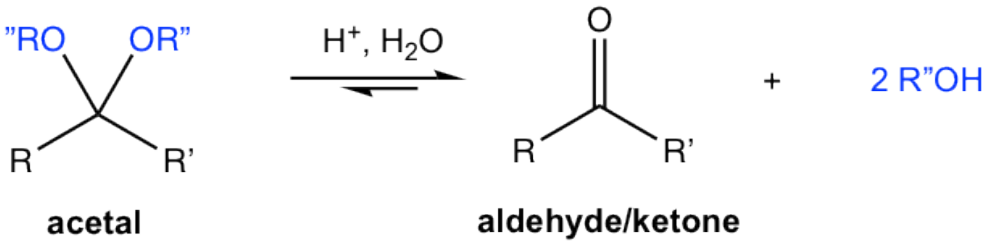
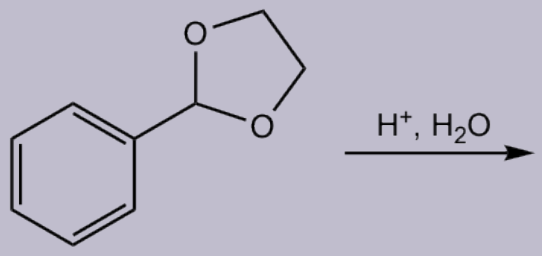


Fig. 2.5f Hydrolysis of Acetal

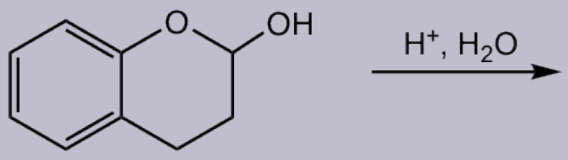
Examples

Show the hydrolysis product of the following reactions:

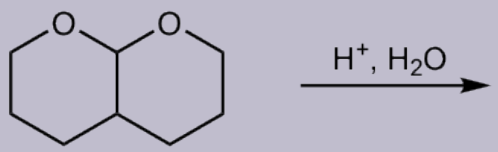
1)



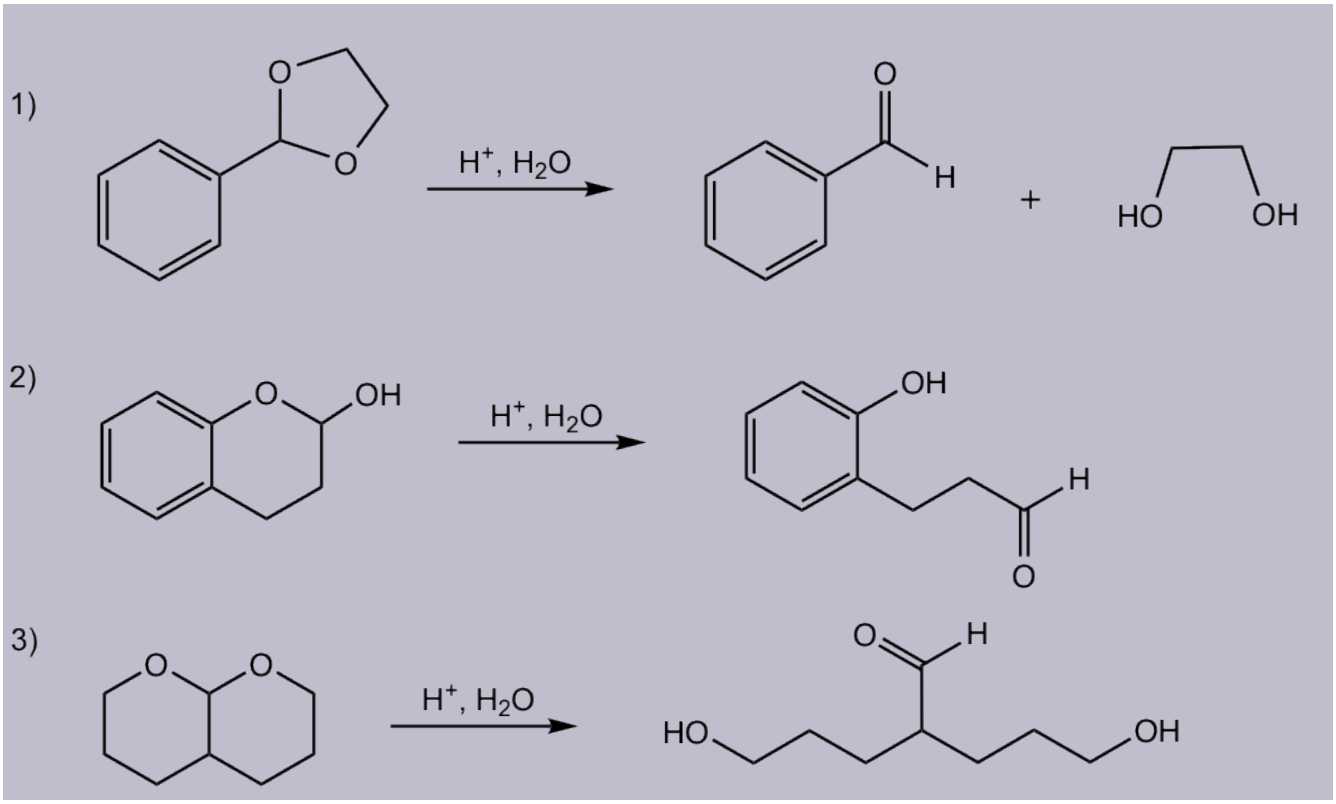
2)



3)

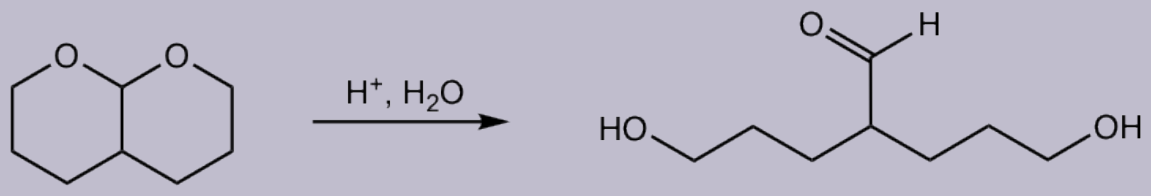


Answers:



Examples

Show the mechanism for the following hydrolysis reaction.

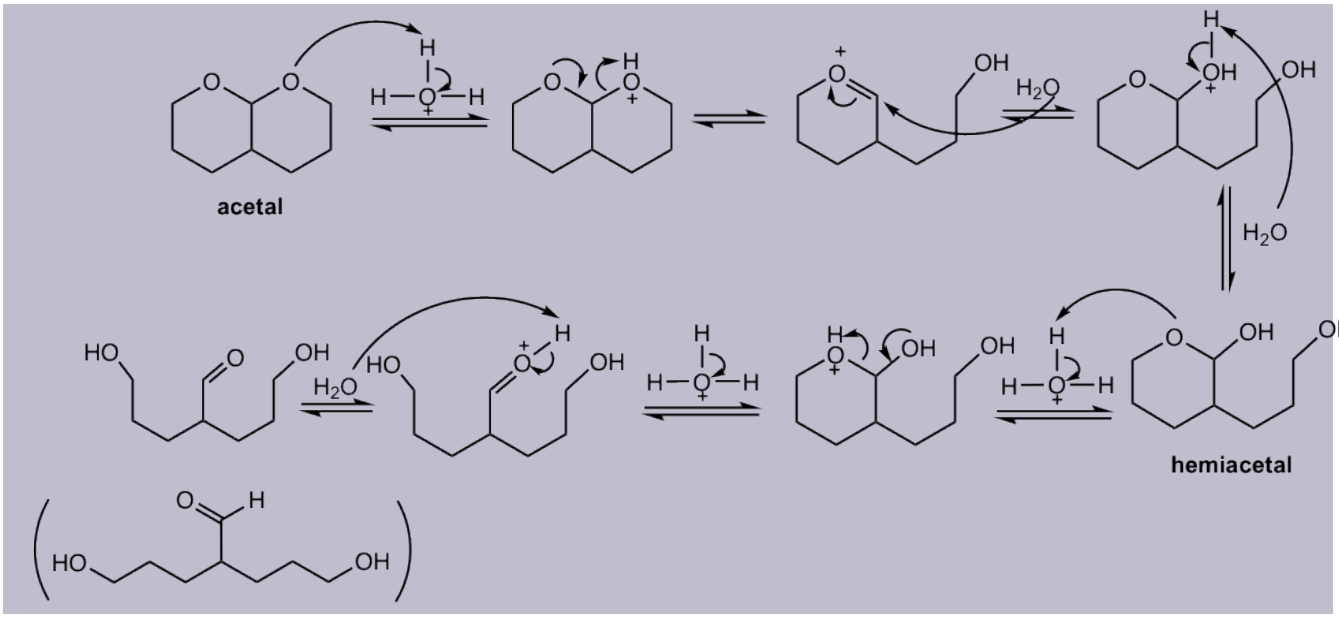


Analysis:

The mechanism for hydrolysis of acetal is just the backward process for the formation of acetal (refer to Fig. and Fig.). The whole process involves seven steps that can be divided into two parts: acetal → hemiacetal, and hemiacetal → aldehyde.

Another trick for this specific question is that the original acetal comes from an intramolecular acetal reaction, which means the carbonyl group and the two OH groups are all involved in the same molecule. Recognition of this point also helps to understand the whole mechanism.

Solutions:



While acetals undergo hydrolysis in an acidic aqueous solution, they are stable and barely undergo any reactions in basic conditions.

2.6 Protecting Groups in Synthesis

In organic synthesis, the strategy of applying a protection group is a very useful technique that has broad applications. The idea of protecting group is that if we would like a reaction to occur only on a "spot" selectively, then the other "spot" could be covered by a ***mask temporarily***. The mask is called the protecting group.

A good choice of protecting group should meet a couple of criteria:

- Easy to put on;
- Unreactive or stable towards further reaction condition;
- Easy to remove

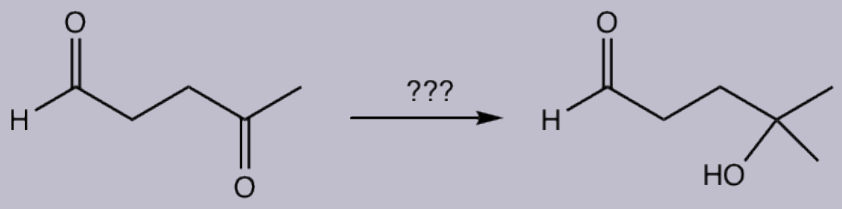
The acetal group, especially the cyclic acetal from diol is a good and common protecting group for aldehyde and ketone. Acetals satisfy all the requirements for good protecting groups:

- The reaction for the formation of acetal can be carried out conveniently, and the reaction occurs selectively with the carbonyl group in aldehyde/ketone.
- The acetal group is stable under basic conditions, that is the reaction condition for nucleophilic addition.
- The acetal group can be easily removed by acidic hydrolysis.

The following example demonstrates the application of protecting group in synthesis.

Examples

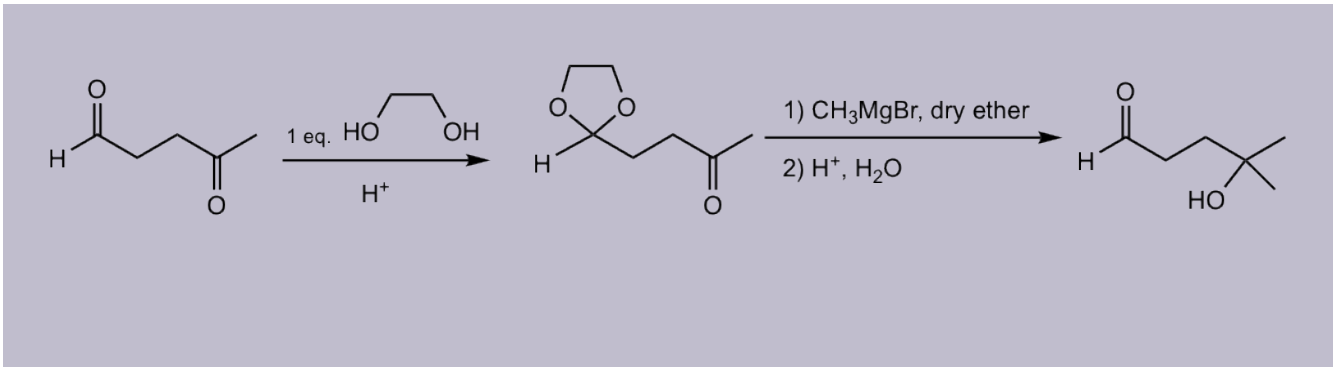
Propose the synthesis route for the following transformation.



Analysis:

Grignard reagent is required for the conversion of ketone to alcohol. However, both aldehyde and ketone react with Grignard reagent, so the aldehyde should be ***protected*** to ensure the reaction occurs only on the ketone site. Because of the higher reactivity of aldehyde, with a limited amount of diol, aldehyde reacts first to get cyclic acetal, the protecting group.

Answer:


1 eq. HO OH
H+
1) CH3MgBr, dry ether
2) H+, H2O
HO

2.7 Addition of Amines and Amine Derivatives to Aldehydes and Ketones

Amine is another type of compound that can do nucleophilic reactions with aldehydes and ketones. Depending on the type of amine reacted, different products are obtained, as summarized below.

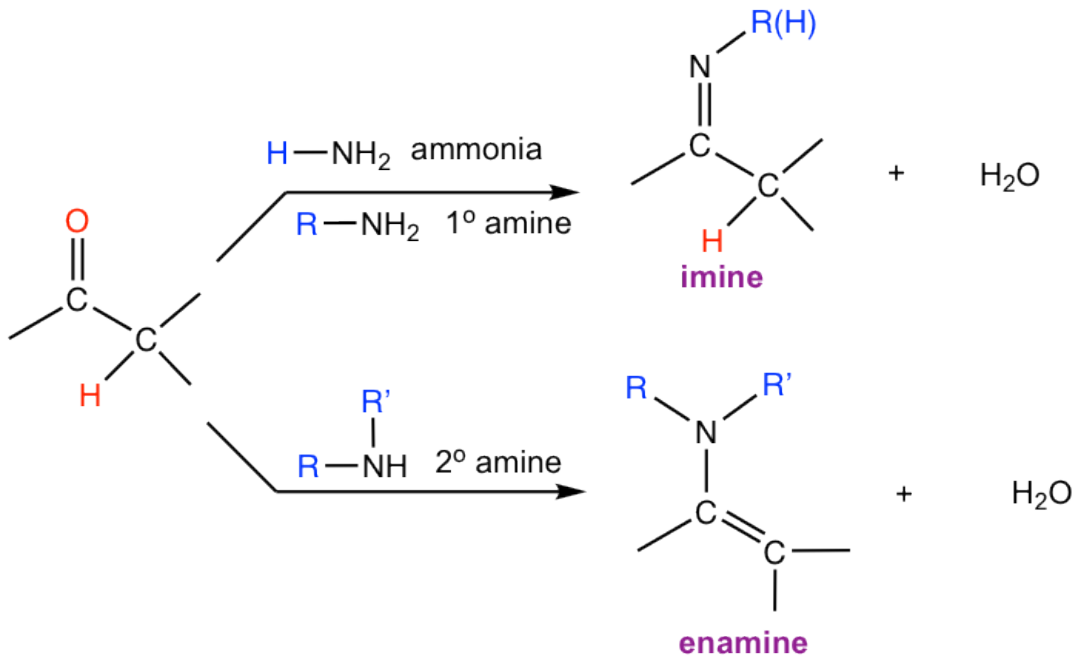


Fig. 2.7a Reactions of amine with aldehydes and ketones

Ammonia or primary (1°) amines react with aldehydes and ketones to produce **imines**, the compound with a C=N double bond.

When secondary (2°) amines react with aldehydes and ketones, **enamines** are formed. Enamine means "alkenamine", that is the compound contains the amino group beside a C=C bond.

2.7.1 Formation of Imines

The pH for reactions that form imine compounds must be carefully controlled in the range of 4 to 5. At low pH (strong acidic) conditions, most of the amine reactant will be protonated and become its ammonium salt, therefore losing the nucleophilicity. If the pH is too high on the other hand, there will not be enough acid (H^+) present to protonate the aminoalcohol intermediate, a key step of converting the OH to the better leaving group H_2O, therefore the reaction will not proceed.

The mechanism for the formation of imine is shown in Fig. 2.7b.

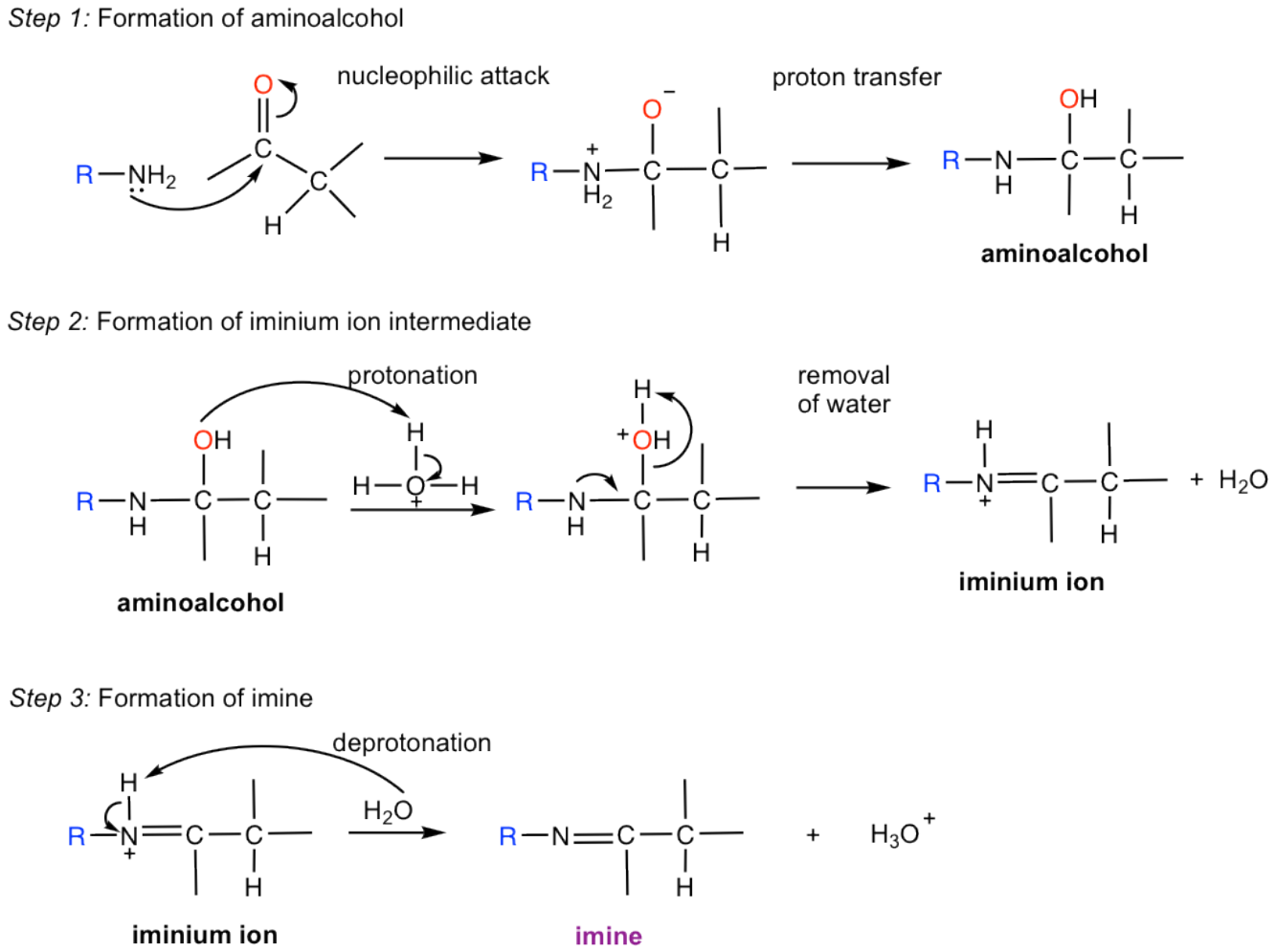


Fig. 2.7b Mechanism for the formation of imine

The overall mechanism for the formation of imine involves multiple steps. It is separated into "three steps" to make it easier to understand and memorize.

Step 1. Amine is the nucleophile and does nucleophilic attack to carbonyl carbon. The resulting intermediate is dipolar, which means N bears a positive charge and O bears a negative charge. A proton transfer then occurs intramolecularly to form a neutral intermediate aminoalcohol. Aminoalcohol can be regarded as the amine analog of acetal, that is NR(H) and OH groups bonded on the same carbon in aminoalcohol.

Step 2. The OH group in aminoalcohol is protonated, allowing it to leave as H_2O. The iminium ion intermediated is formed after dehydration (removal of H_2O).

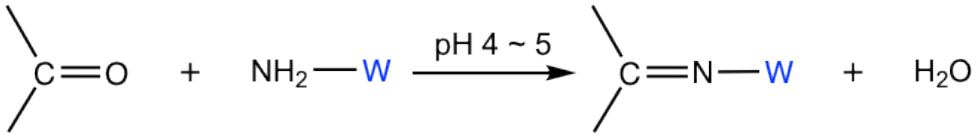
Step 3. The H bonded on nitrogen is deprotonated to give the neutral imine product.

Hint: To figure out the structure of the imine product, replace the O atom in aldehyde or ketone with the N atom, and remember to keep the R group (or H for ammonia) in the amine reactant as well.

2.7.2 Imine Derivatives

The reaction between aldehyde/ketone and primary amines can be extended to a group of other compounds. The structures of these compounds all fit into the general formula of NH_2-W (similar to the formula of primary amine). These compounds react with aldehyde/ketone in a similar way as primary amines do and form a series of products containing the C=N bond, that are called **imine derivatives**. The names and structures of the group of compounds, together with the imine derivative products are summarized in Table 2.2 below.

General Reaction



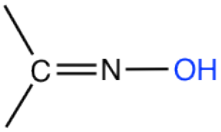
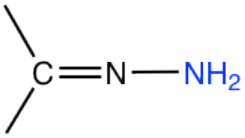
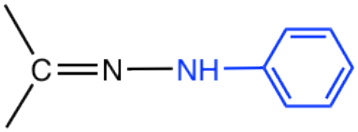
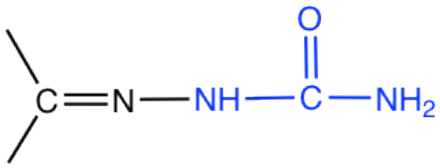
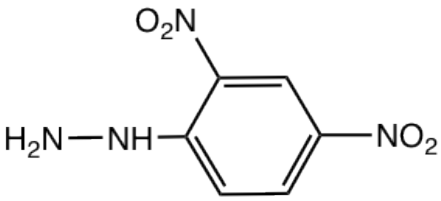
NH_2—W		Imine Derivatives	
NH_2OH	hydroxyamine		**oxime**
NH_2NH_2	hydrazine		**hydrazone**
$NH_2NHC_6H_5$	phenylhydrazine		**phenylhydrazone**
$NH_2NHCONH_2$	semicarbazide		**semicarbazone**

Table 2.2 Formation and Structures of Imine Derivatives

These imine derivatives are usually crystalline solids that have sharp and characteristic melting points. Such properties were used to be applied as a method to determine the identification of unknown carbonyl compounds. The melting point of the imine derivative of any known is determined and compared with the melting point of the same derivative of a known compound in a reference. Such a method was especially useful before the broad application of the spectroscopy technique.

2,4-dinitrophenylhydrazine, a specific phenylhydrazine that is called **Brady's reagent,** is still used as a reagent to

detect the presence of aldehyde or ketone. The reaction of Brady's reagent with aldehyde or ketone produces a bright precipitate of yellow, orange, or red color.



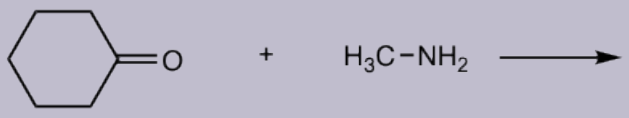
Brady's reagent

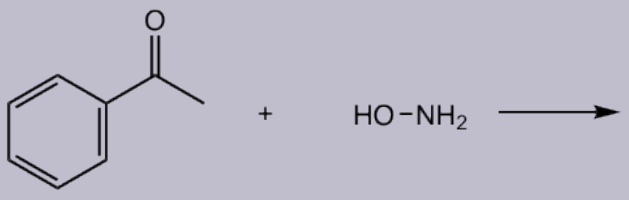
2,4-dinitrophenylhydrazine

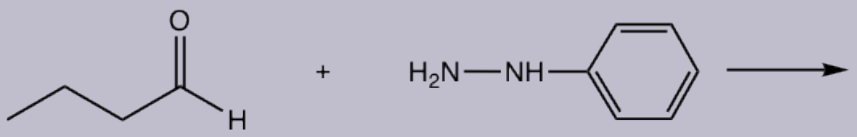
Fig. 2.7c Brady's reagent

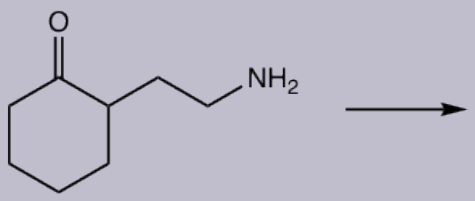
Examples

Show the product of imine or imine derivatives for the following reactions.

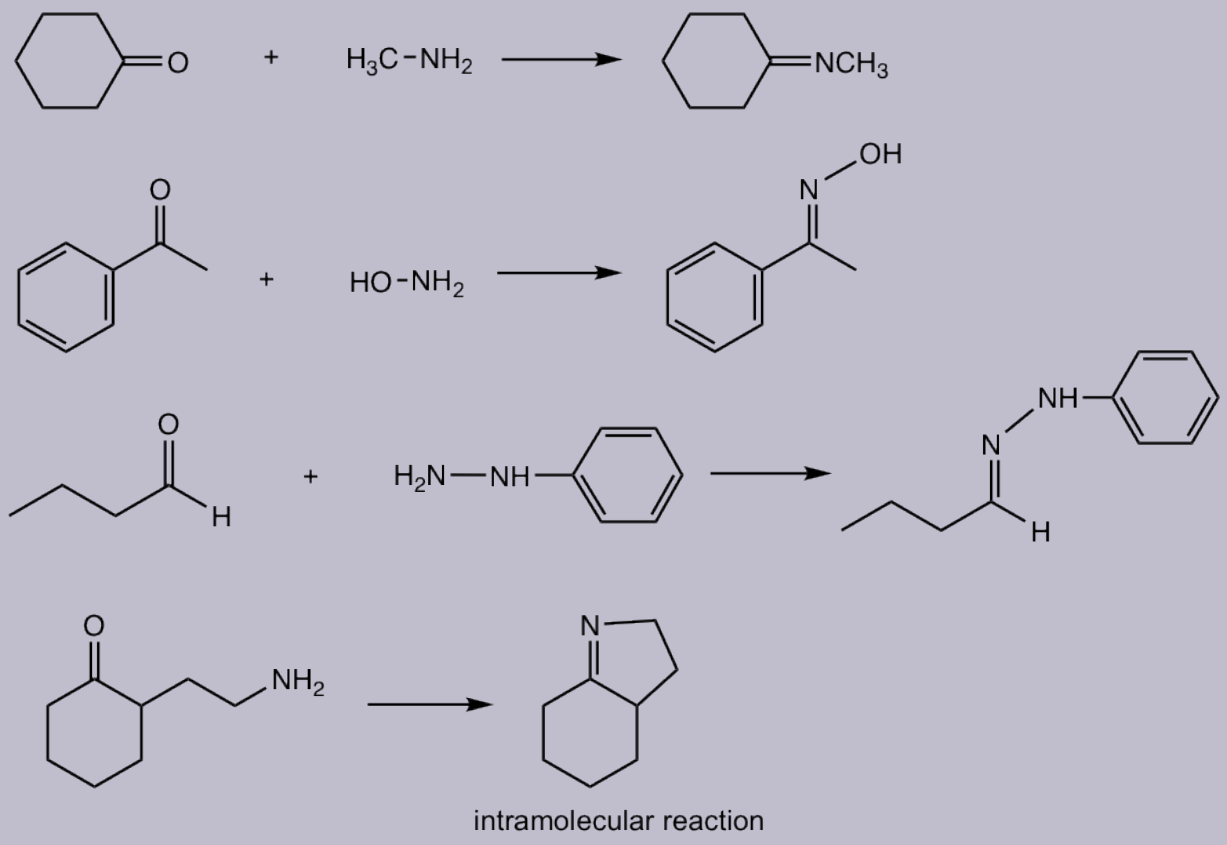








Answers:



Wolff-Kishner Reduction

The hydrazone derivatives of ketones can be further reduced to alkane when reacted in a strong base condition with KOH at a very high temperature. The reaction is called **Wolff-Kishner Reduction,** a common method to do deoxygenation of the carbonyl group, and reduce ketone to alkane directly. The reaction proceeds well with the mixture of ketone, hydrazine, and base heated together. No isolation of the hydrazone intermediate is necessary.

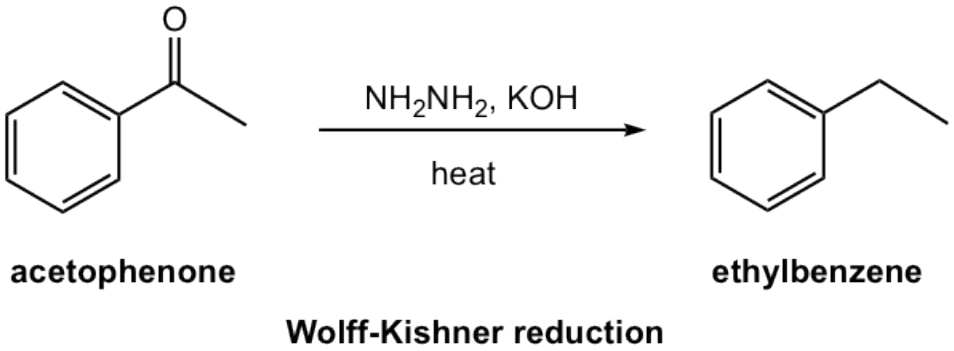
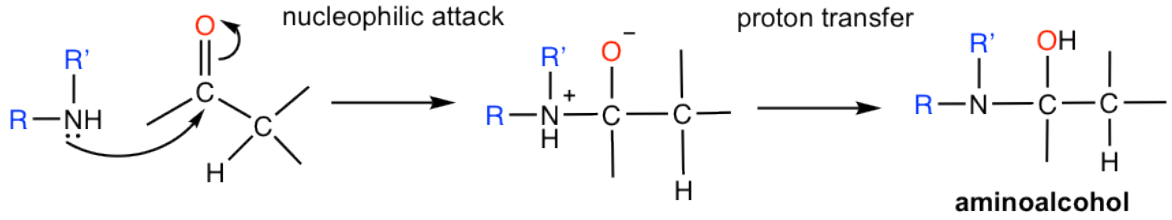


Fig. 2.7d Wolff-Kishner reduction to reduce acetophenone (methyl phenyl ketone) to ethylbenzene

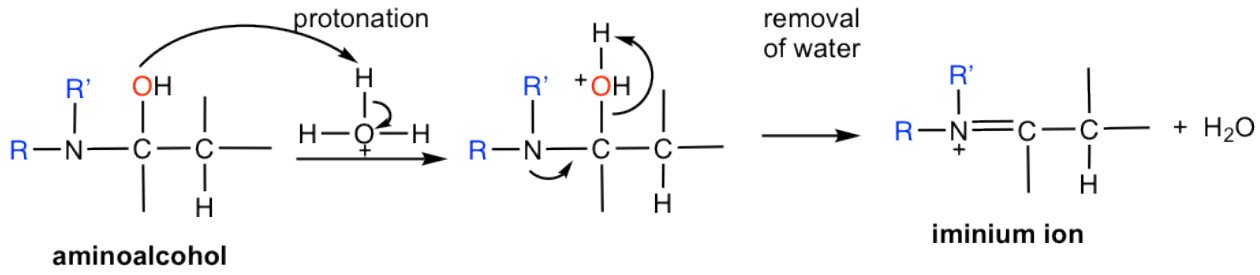
2.7.3 Enamines

The reaction of secondary (2°) amines with the carbonyl group proceeds in the different mechanisms and forms enamine. The reason for the product difference is simply because there is one less hydrogen in 2° amines. See the mechanism in Fig. 2.7e for details.

Step 1: Formation of aminoalcohol



Step 2: Formation of iminium ion intermediate



Step 3: Formation of enamine

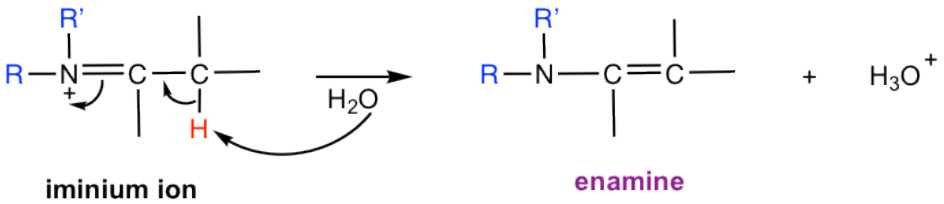
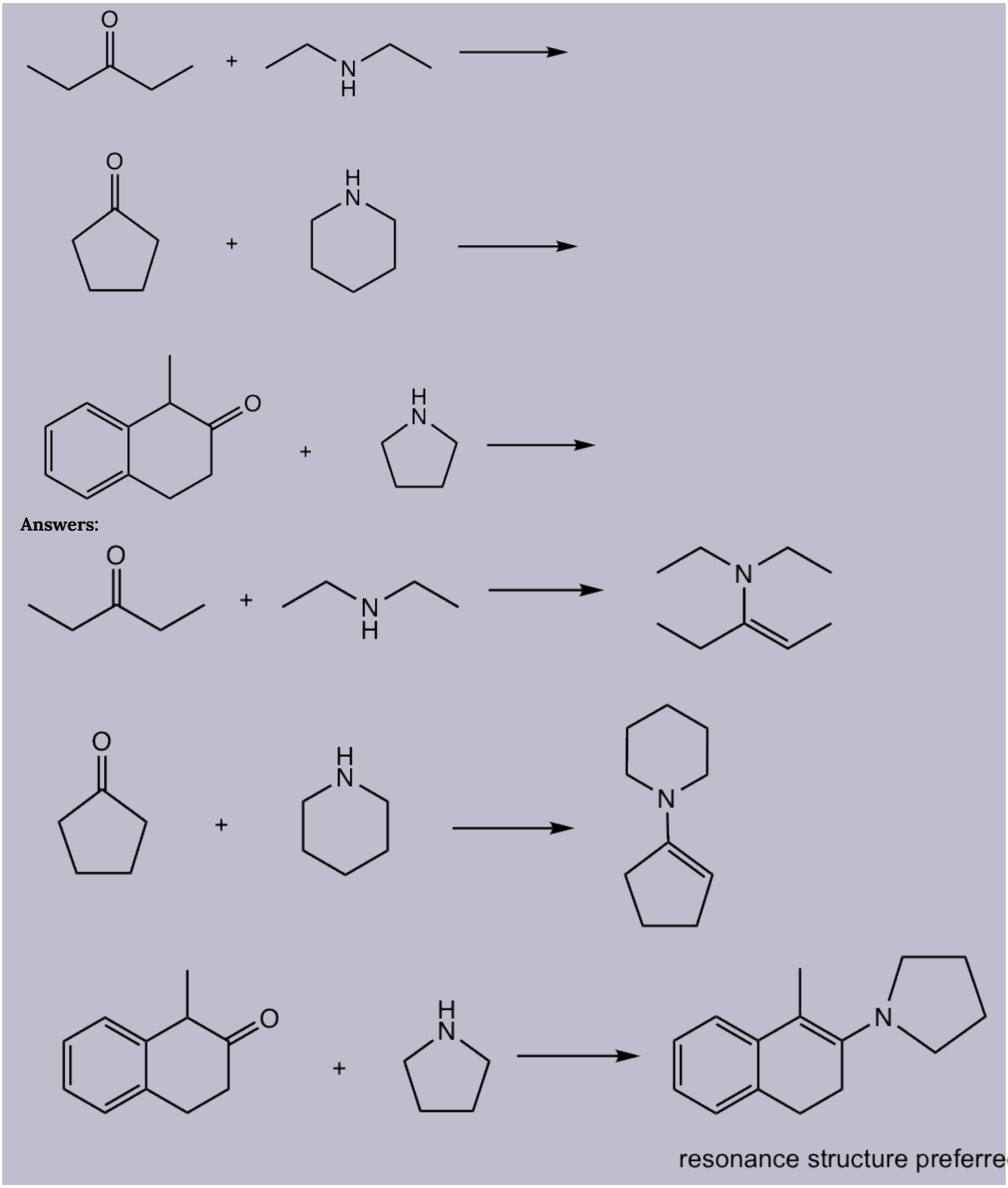


Fig. 2.7e Mechanism for the formation of enamines

Comparison between the mechanism for the formation of **imine** (Fig. 2.7.b) and that of **enamine** revolves that the first two steps (up to the formation of iminium ion intermediate) are the same. The only difference lies in the last deprotonation step. Since there is no H available on the nitrogen atom for removal for 2°amine, the proton has to be removed from the adjacent carbon, resulting in the enamine.

Examples

Show the product of the following reaction.


O
+
N
H
O
+
H
N
O
+
H
N
Answers:
O
+
N
H
N
O
+
H
N
N
O
+
H
N
N
resonance structure preferred

2.8 Wittig Reaction

Wittig reaction is a type of interesting reaction with great applications. In this reaction, we will also encounter a new reagent which is called phosphorus ylide. This reaction is named for George Wittig who was awarded the Nobel prize for this work in 1979. The general equation of the Wittig reaction is shown below, with a specific example.

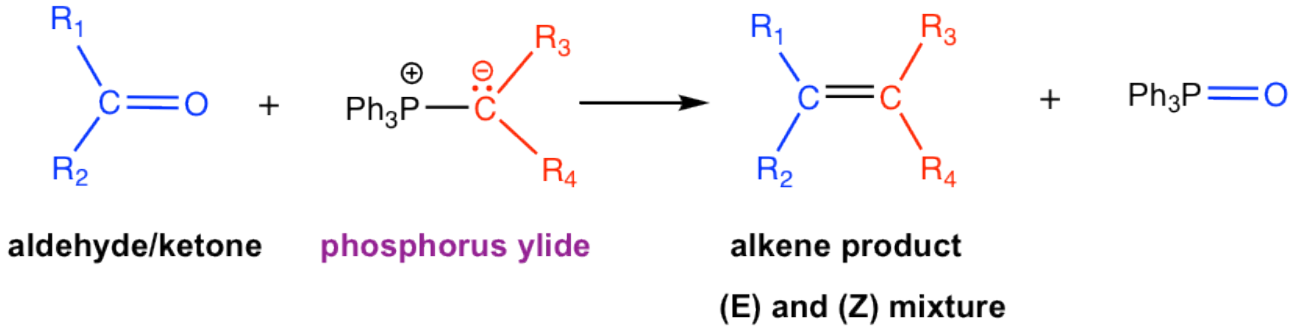


Fig. 2.8a General Wittig reaction equation

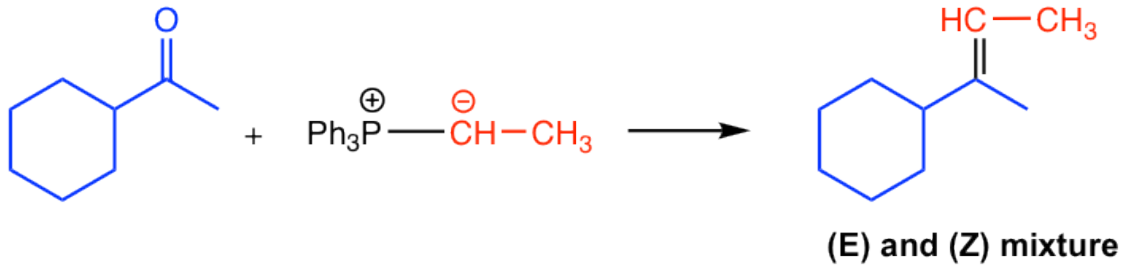


Fig. 2.8b Wittig reaction example

Wittig reaction provides a method for synthesizing alkene from aldehyde or ketone, by adding more carbons in the product. The product alkene can be regarded as an "add-up" by connecting the carbon-containing parts from both reactants together (blue plus red) via a double bond. Another great benefit of the Wittig reaction is that the location of the double bond is fixed, compared with other methods for the preparation of alkene, for example, E1, in which the mixture of constitutional isomers is obtained due to rearrangement. The reaction therefore can be designed by picking up the reactants that bear certain substituents that match the structure of the desired product.

The overall Wittig reaction involves two parts:

- Preparation of phosphorus ylide on site;
- Reaction of aldehyde or ketone with phosphorus ylide

The phosphorus ylide should be prepared freshly on site, without separation though. Freshly prepared ylide can then be mixed with carbonyl compound in the same reaction vessel, and the reaction can be accomplished in several hours. Therefore it is practically easy to carry out the Wittig reaction. Although practically it is not necessary to separate the phosphorus ylide, the overall reaction mechanism will still be discussed in two parts, for learning purposes.

Mechanism for the preparation of phosphorus ylide

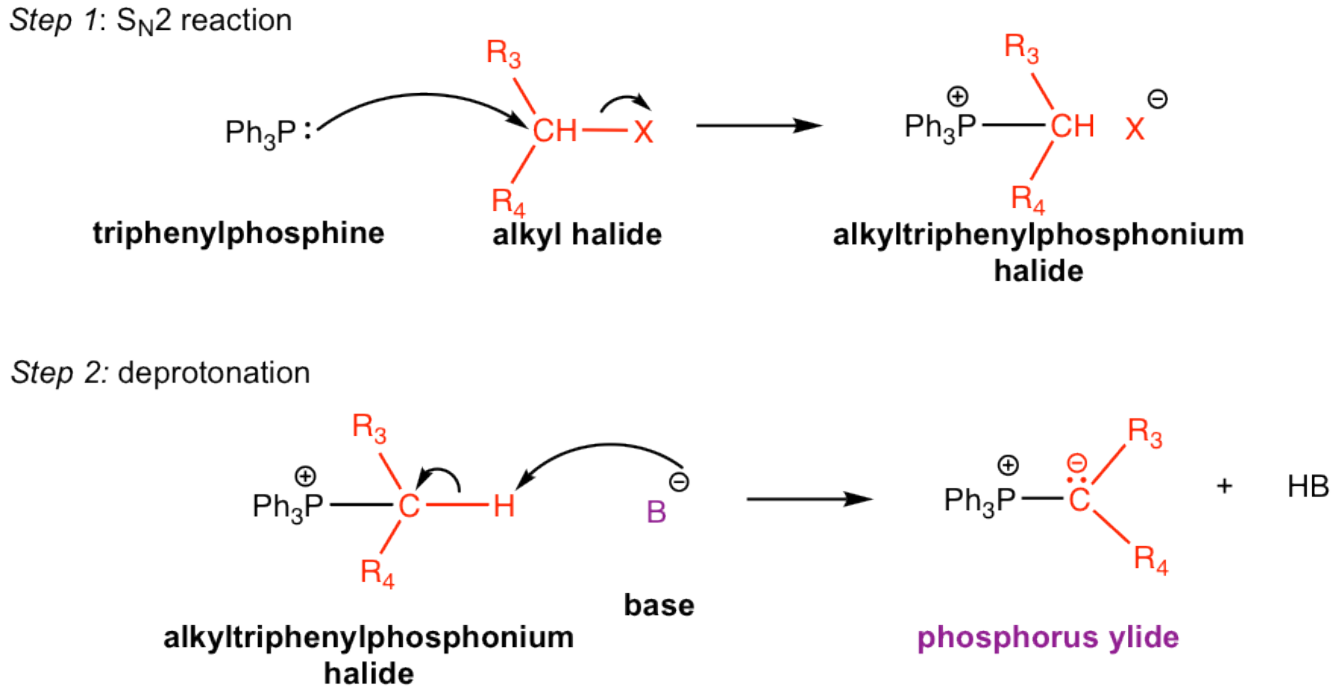


Fig. 2.8c Mechanism for the preparation of phosphorus ylides (**Note: It is optional to show the lone pair electron on the carbon atom in the structure of Ylide. Whether the lone pair is shown or not, you should understand that the carbon atom with a negative charge does bear the lone pair electron.)**

The preparation of phosphorus ylide involves two steps. The first step is a S_N2 reaction, that the alkyl halide reacts with nucleophile triphenylphosphine (PPh_3). PPh_3, with the electron pair on the phosphorus element, is an excellent nucleophile due to the relatively large size of phosphorus and reacts readily with 1° and 2° alkyl halides by S_N2 reaction. The S_N2 reaction product, a phosphonium halide salt, is then deprotonated by a strong base in the second step to produce the phosphorus ylide. Organolithium compound and amide (NH_2^-) are usually used as bases in the second step. Even though the reaction proceeds with two steps, practically the alkyl halide, triphenylphosphine, and base can be mixed all together to prepare the phosphorus ylide.

Sometimes the resonance structure involves the C=P double bond is also used as the structure for phosphorus ylide. The quantum mechanical calculation indicates, however, that the charge separation structure is the major contributor.

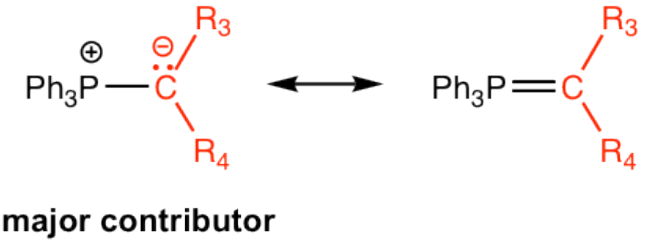
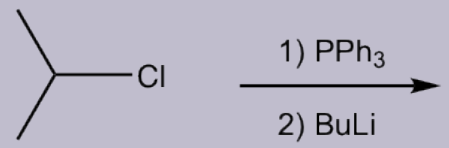


Fig. 2.8d Resonance structures of phosphorus ylide

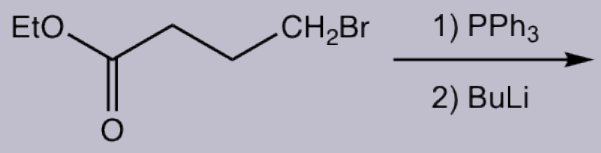
Examples

Show the structure of the ylides produced.

1)

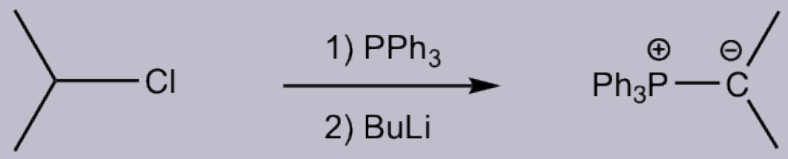


2)

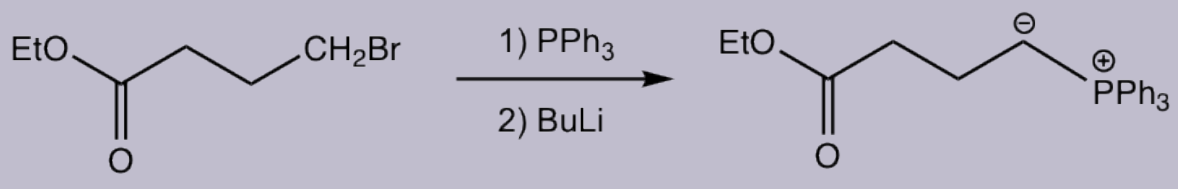


Answers:

1)



2)



Mechanism for the Wittig reaction of phosphorus ylide with aldehyde/ketone

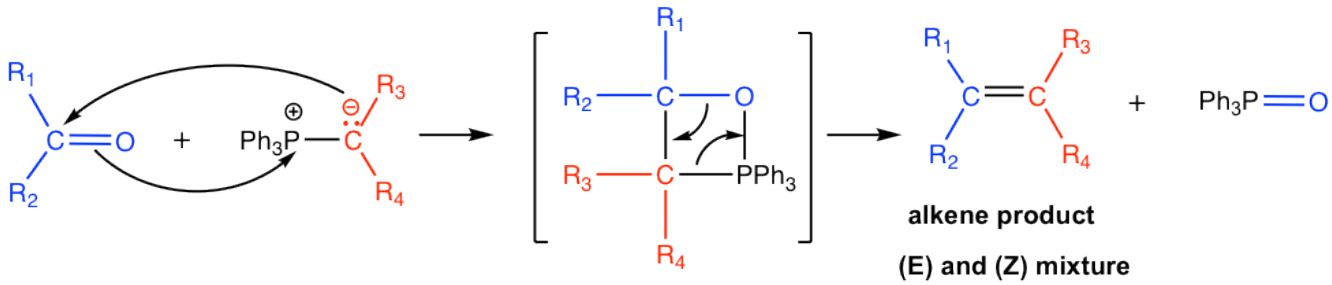


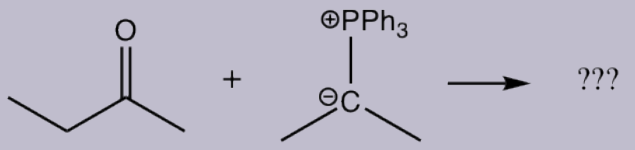
Fig. 2.8e Mechanism for the Wittig reaction

When phosphorus ylide reacts with the carbonyl group in aldehyde/ketone, a four-membered ring intermediate is first formed by the cycloaddition. Then the ring decomposes to form alkene and triphenylphosphine oxide, $Ph_3P{=}O$. The formation of the very strong phosphorus-oxygen bond in $Ph_3P{=}O$ is the driving force for the reaction.

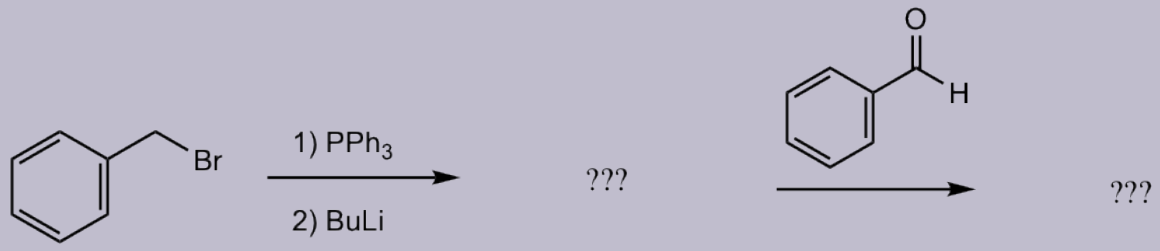
Examples

Fill up the product or the missing reactant/reagents for the following reactions.

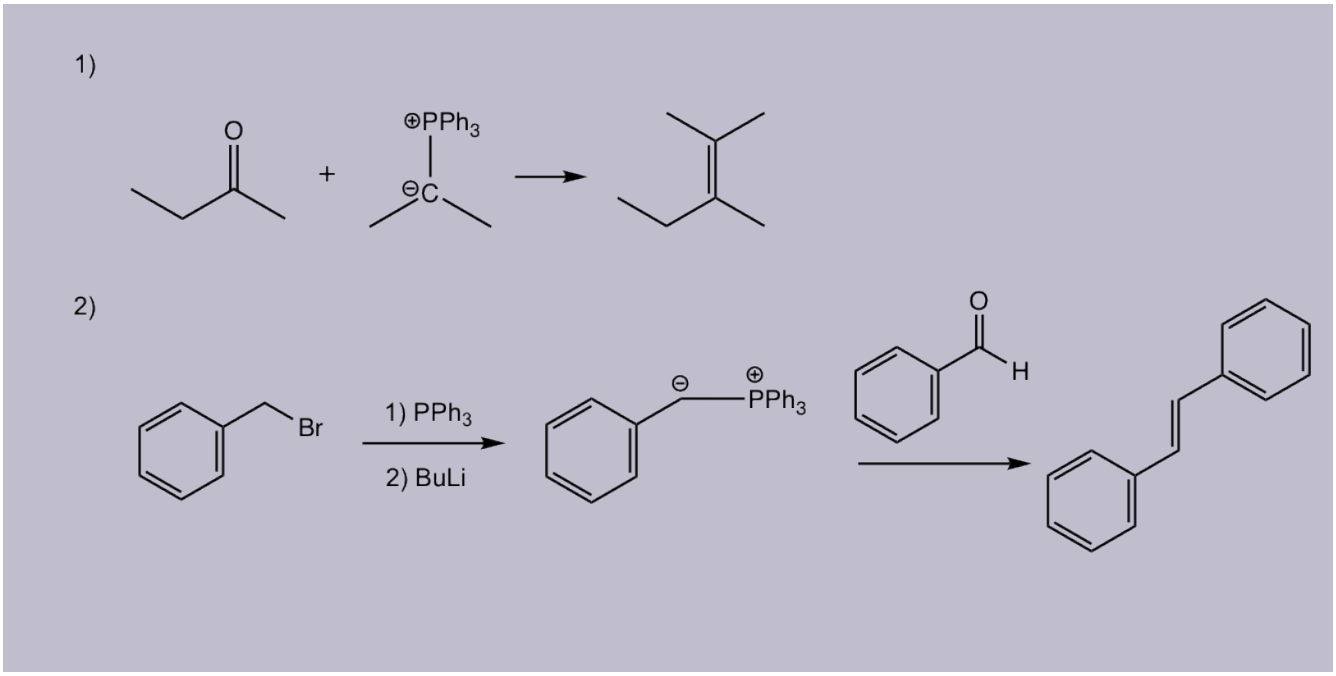
1)



2)



Answers:

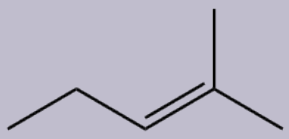


Plan a Wittig Synthesis

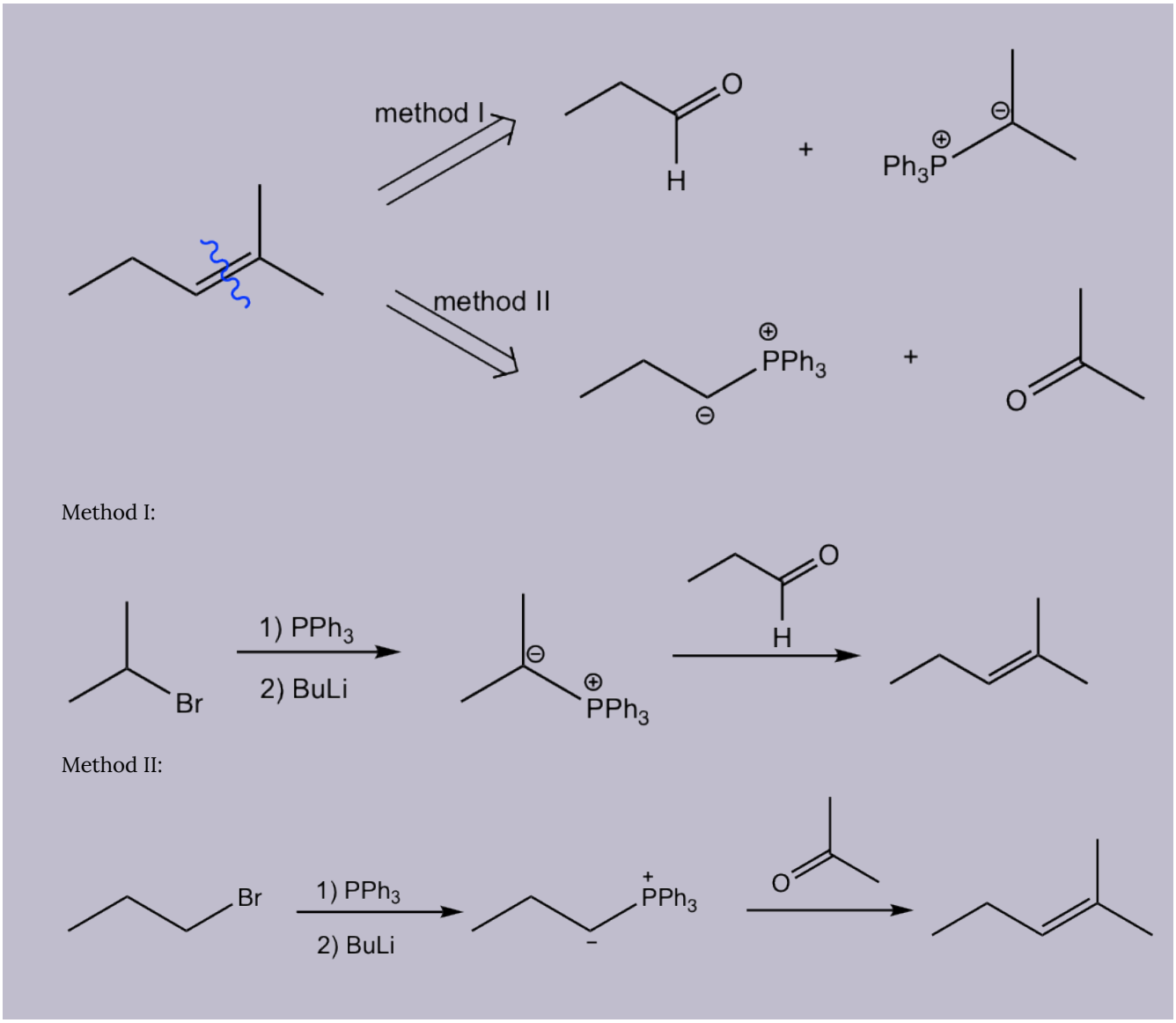
Based on the structure of the desired alkene product, the synthesis route can be designed by choosing the proper aldehyde/ketone and alkyl halide for ylide.

Examples

Design synthesis of the following compound using a Wittig Reaction.



Analysis:



Method I:

Method II:

2.9 Baeyer-Villager Reaction

Baeyer-Villager reaction is the oxidation of an aldehyde or ketone by applying peroxycarboxylic acid as the oxidizing agent. In Baeyer-Villager reaction, the aldehyde is oxidized to carboxylic acid, and the ketone is oxidized to an ester. A couple of examples are given in Fig. 2.9a.

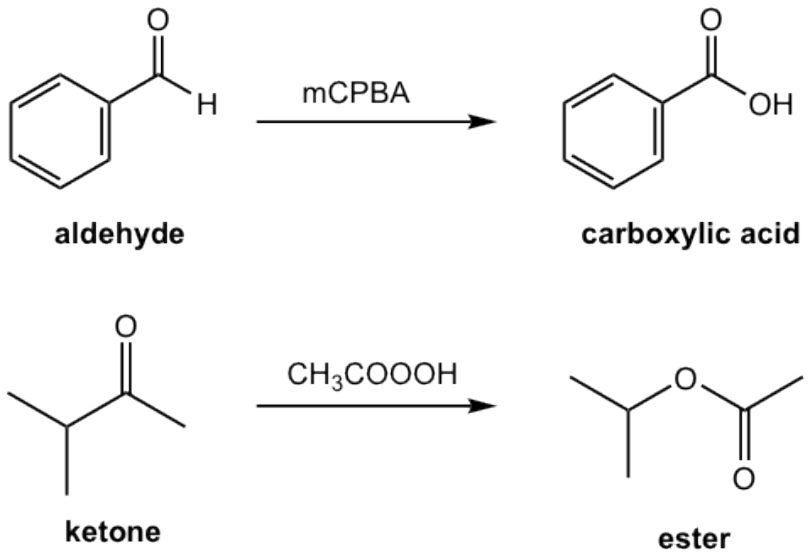
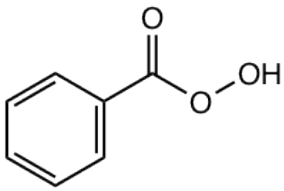


Fig. 2.9a Baeyer-Villager reaction examples

Peroxycarboxylic acid is a strong oxidizing agent, which has the peroxy group O-O. A common peracid used for Baeyer-Villager reaction is *m*-chloroperoxybenzolic acid, or *m*CPBA.



***m*-chloroperoxybenzolic acid (*m*CPBA)**

Fig. 2.9b The structure of mCPBA

The mechanism for Baeyer-Villager reaction is shown in Fig. 2.9c.

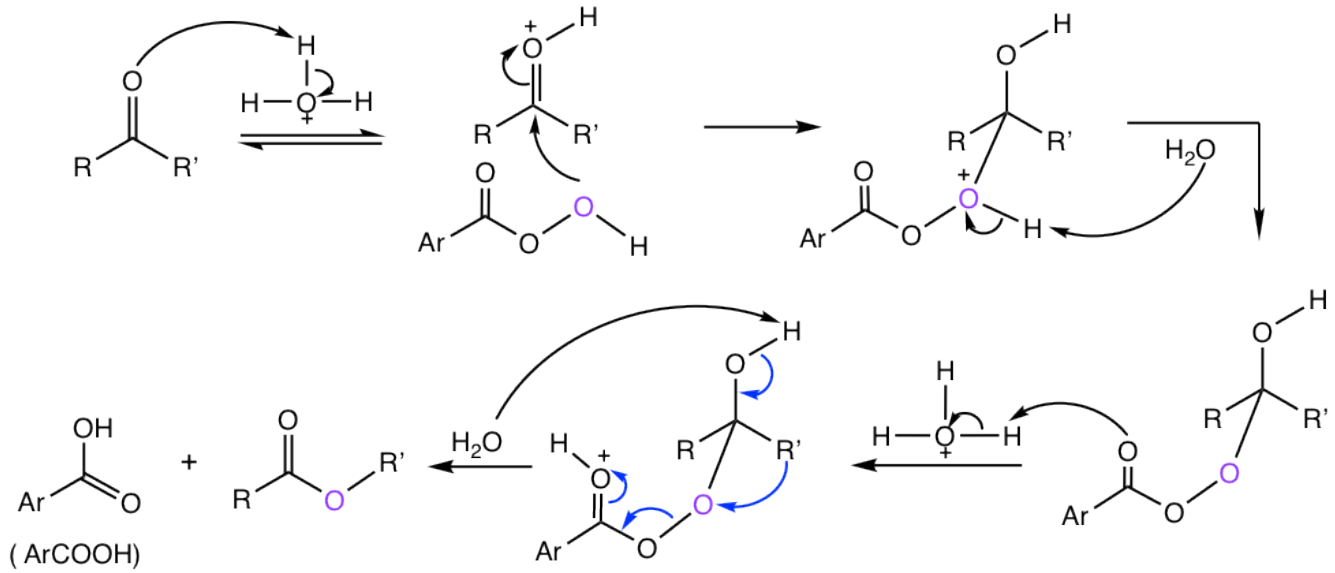
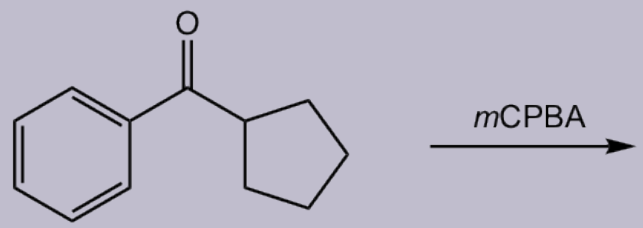


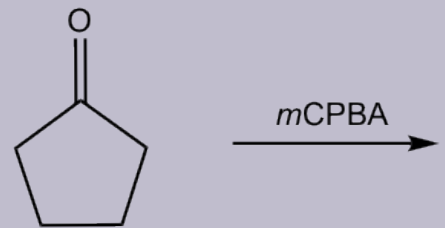
Fig. 2.9c Mechanism for Baeyer-Villager reaction

The group (R' in the mechanism in Fig. 2.9c) migration is the key step in the mechanism. Different group has different tendencies for migration. It is shown from studies that the aptitude for migration is: **H > Ar > 3° > 2° > 1° > methyl**. For aldehyde, H migrates and results in carboxylic acid. For ketone, the migration group R' will be the OR' in the ester product.

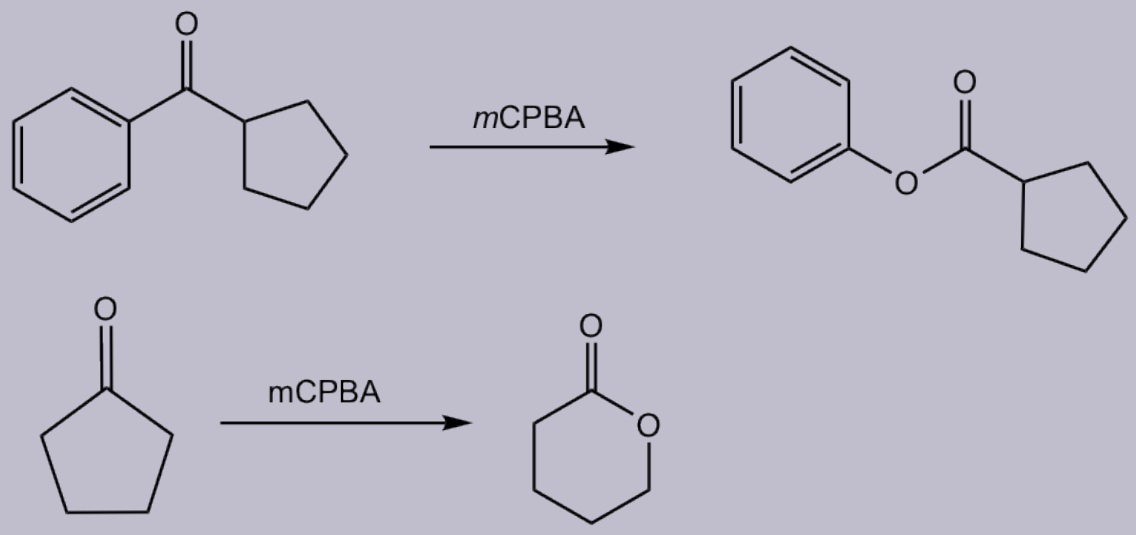
Examples

Show the product of the following reactions.



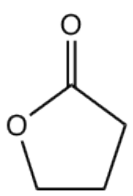


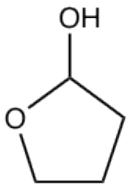
Answers:

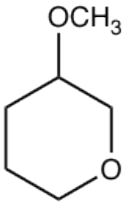


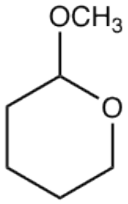
2.10 Practices

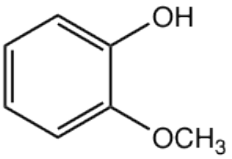
1. Label hemiacetal or acetal in the following structure

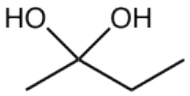


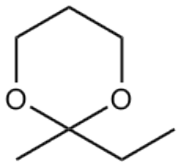


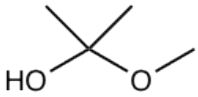






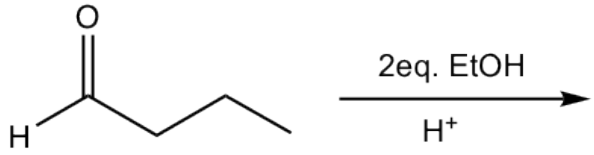




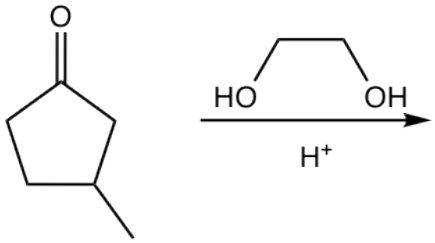


2. Show the product of the following reactions.

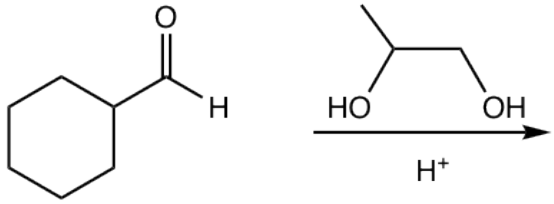
a.



b.



c.



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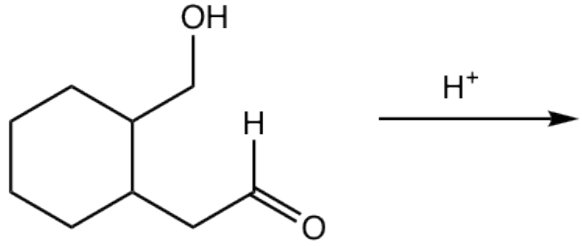

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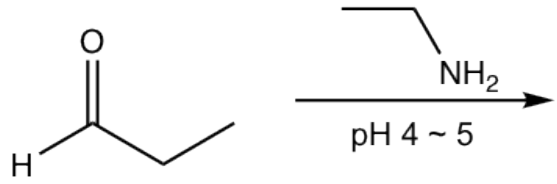

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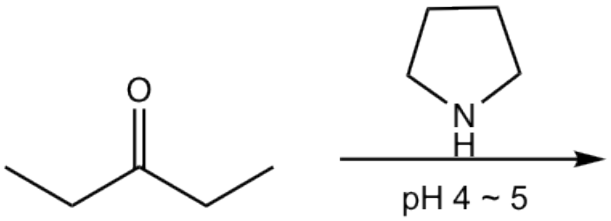

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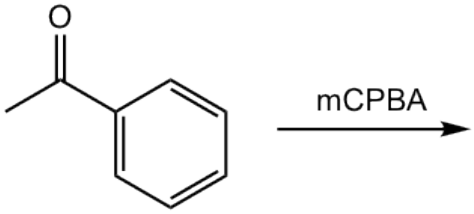

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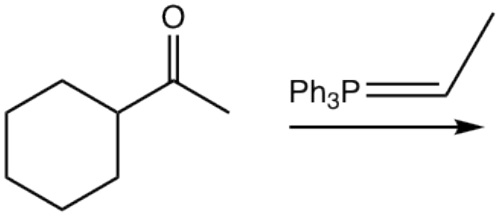
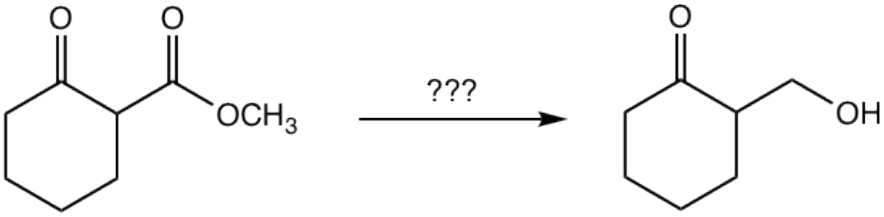
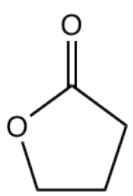


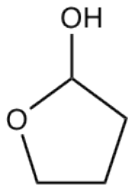
3. Show the detailed steps for the following synthesis.



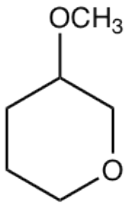
2.11 Practices Answers

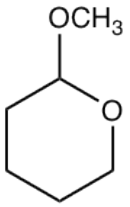
1. Label hemiacetal or acetal in the following structures.



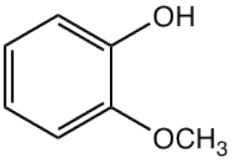


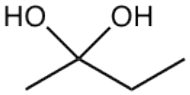
hemiacetal

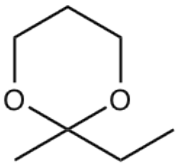




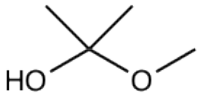
acetal







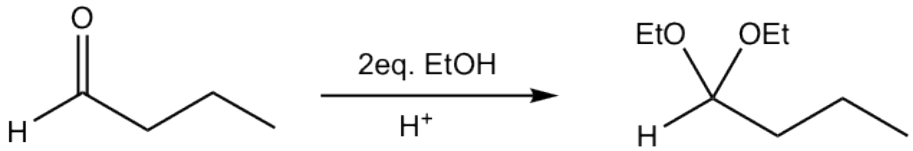
acetal



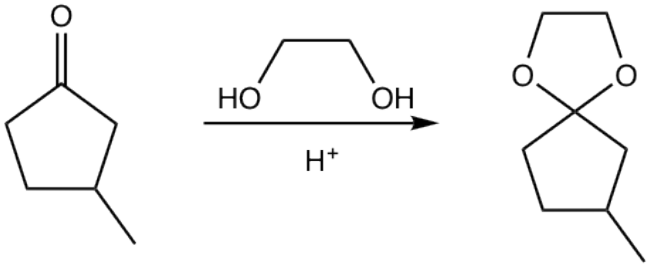
hemiacetal

2. Show the product of the following reactions.

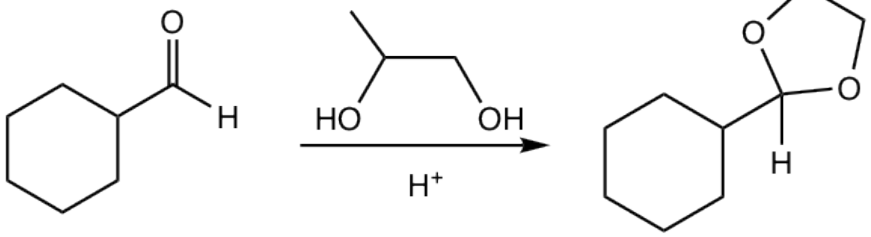
a.



b.



c.



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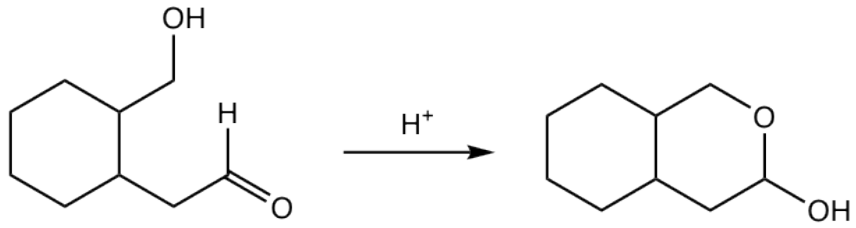

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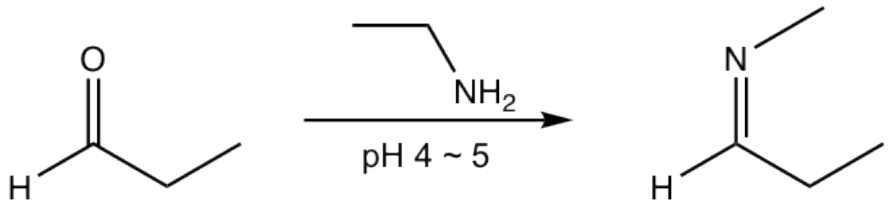

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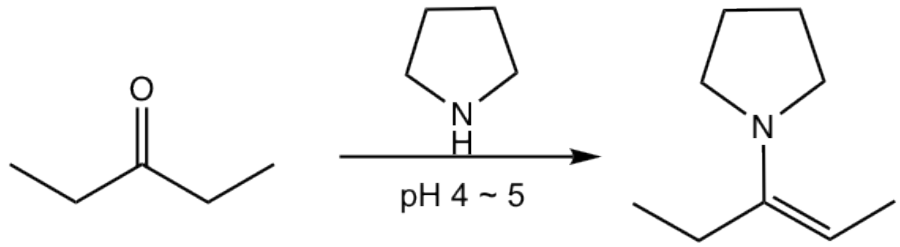

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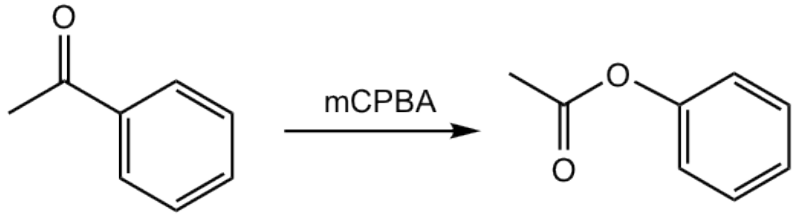

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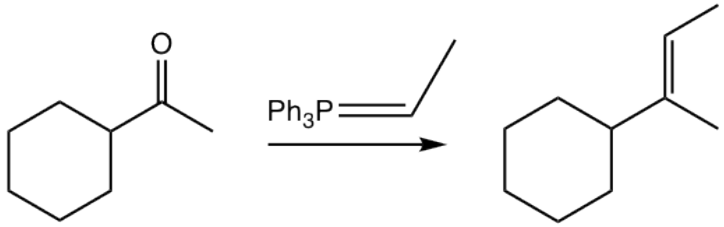
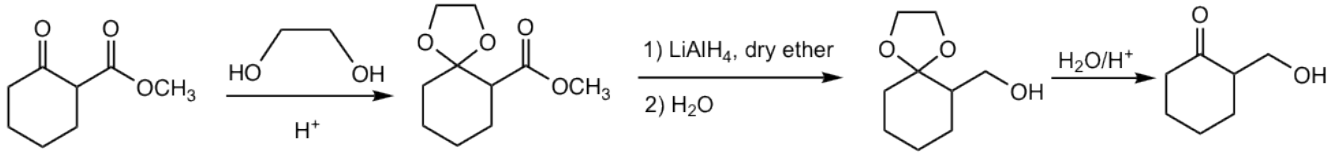


3. Show the detailed steps for the following synthesis.

Tips: $LiAlH_4$ reduces ester to alcohol, however it reduces the ketone group as well. To ensure the reaction occurs only on the ester group selectively, the ketone group could be first protected by cyclic acetal, then deprotected after the reduction. So three steps are necessary for the overall synthesis, as shown below.



CHAPTER 3: CONJUGATED UNSATURATED SYSTEMS

To introduce the conjugated system, let's first take a look at a reaction.

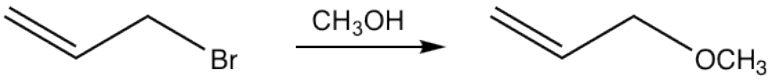


Fig. 3a Substitution reaction of allyl bromide

This is a substitution reaction, and it proceeds well with good yield. The question is whether the reaction goes through S_N1 or S_N2 mechanism. The weak nucleophile CH_3OH seems like a suitable choice for S_N1, but the primary bromide substrate has a high tendency to go with S_N2. What is the correct answer then?

It turns out that the reaction goes with the S_N1 mechanism, with the stable allyl carbocation involved as the intermediate. The allylic position is the carbon which is adjacent to a C=C double (π) bond. Although it is a primary carbocation, the allyl carbocation shows special stability. Studies indicate that allyl carbocation is even more stable than a 2° carbocation and is almost as stable as a 3° carbocation due to the resonance stabilization effect of the double bond.

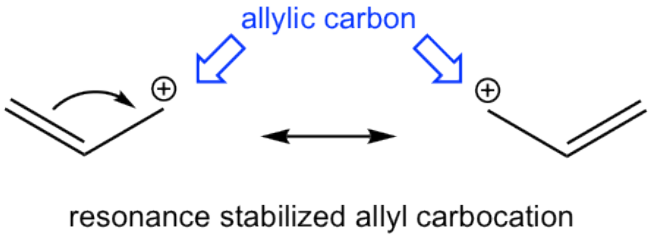


Fig. 3b Allyl carbocation stabilized by resonance effect

Another example of the special reactivity on allylic position is the radical halogenation of propene, in which allyl radical is the intermediate involved. Allylic hydrogens are especially reactive in radical substitution reactions, despite the fact that they are bonded on a primary carbon.

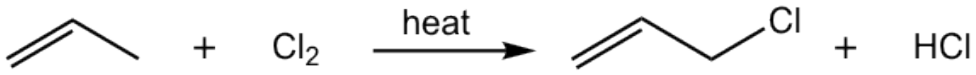


Fig. 3c Radical halogenation of propene

The reason for the special stability of allyl carbocation and allyl radical is that they both belong to a special system called the **conjugated system.** The special properties and reactivities of the **conjugated system** are the topics for this chapter.

3.1 Simplest Conjugated System: Allyl System

Structure Features of Allyl System

In the structure of allyl carbocation, both double carbons are in sp^2 hybridization, with an unhybridized 2p orbital perpendicular to the hybrid orbitals as shown in Fig. 3.1a. There is one electron in the 2p orbital for each of the double-bond carbon. The carbon that bears a positive charge is also in sp^2 hybridization, with the same set of orbitals, however the 2p orbital is empty. **So there are a total of two π electrons in allyl carbocation.**

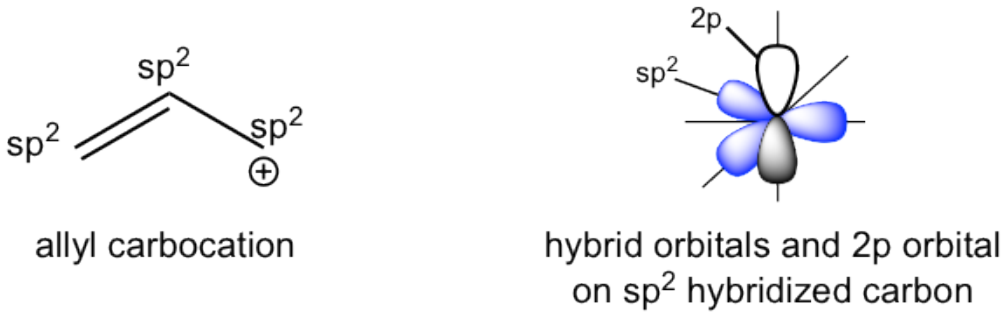


Fig. 3.1a Orbitals of allyl carbocation

***When there is at least one atom with p orbital adjacent to at least one π bond*, the whole system is a conjugated system**. The allyl carbocation, with three p orbitals in total, fits in the definition and is an example of the simplest conjugated system, the allyl system.

Besides the allyl carbocation, the allyl system also includes allyl radical and allyl carbon anion. Each of the allyl species has three p orbitals, but the number of π electrons is different. There are two π electrons in allyl carbocation, three π electrons in allyl radical, and four π electrons in allyl carbon anion.

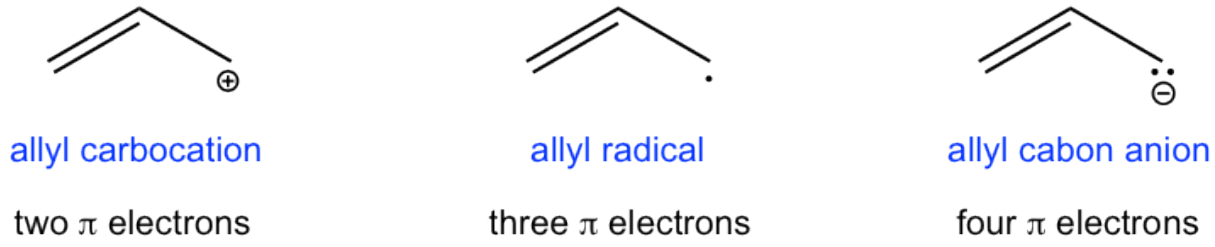


Fig. 3.1b Three allyl species

The understanding of the special stability of the allyl system species can be achieved in two ways: resonance stabilization effect theory or molecular orbital theory.

Resonance Stabilization Effect Theory for Allylic System

The stability a species gains from having charge delocalization through resonance contributors is called the ***resonance stabilization effect*** (refer to **section 1.3 in Book I**). All the allyl species have two equivalent resonance structures, and the actual structure is a hybrid of the two. Charges (or single electrons) can be delocalized to the other carbon as well, instead of just staying on one spot, therefore the whole allyl species has special stability.

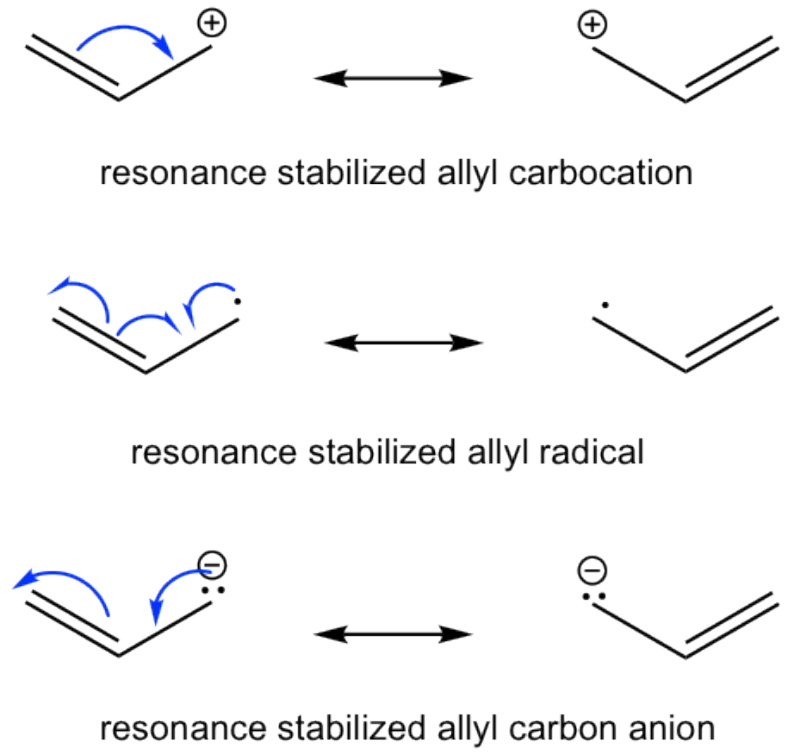

resonance stabilized allyl carbocation
resonance stabilized allyl radical
resonance stabilized allyl carbon anion

Fig. 3.1c Resonance structures of the three allyl species

Molecular Orbital Theory for Allyl System

Molecular orbital (MO) theory focuses on the combination of atomic orbitals to form new molecular orbitals. When atomic orbitals combine to form molecular orbitals, the number of MOs always equals the number of atomic orbitals that combine. When atomic orbitals combine with the same phase, a **bonding molecular orbital** is formed; and the overlap of two atomic orbitals with opposite phases results in the **antibonding molecular orbital**. The energy of electrons in a bonding MO is less than that in the separate atomic orbital, and the energy of electrons in an antibonding MO is greater than that in the atomic orbital. The nonbonding MO is in the same energy level as the atomic orbital. All the rules for assigning electrons to atomic orbitals also apply to molecular orbitals.

For allyl systems, we will just consider the p molecular orbitals that arise from the combination of p atomic orbitals. Since each carbon atom has one 2p orbital, there total of three 2p orbitals. The combination of them results in three π molecular orbitals, that is bonding, nonbonding, and antibonding orbitals (Fig. 3.1d). The nonbonding π MO has a node (nodal plane) at the middle carbon, and the antibonding π MO has two nodes (nodal planes) that separate the opposite phases of the lobes. The simplified sketching of the π MOs is shown in the diagram below.

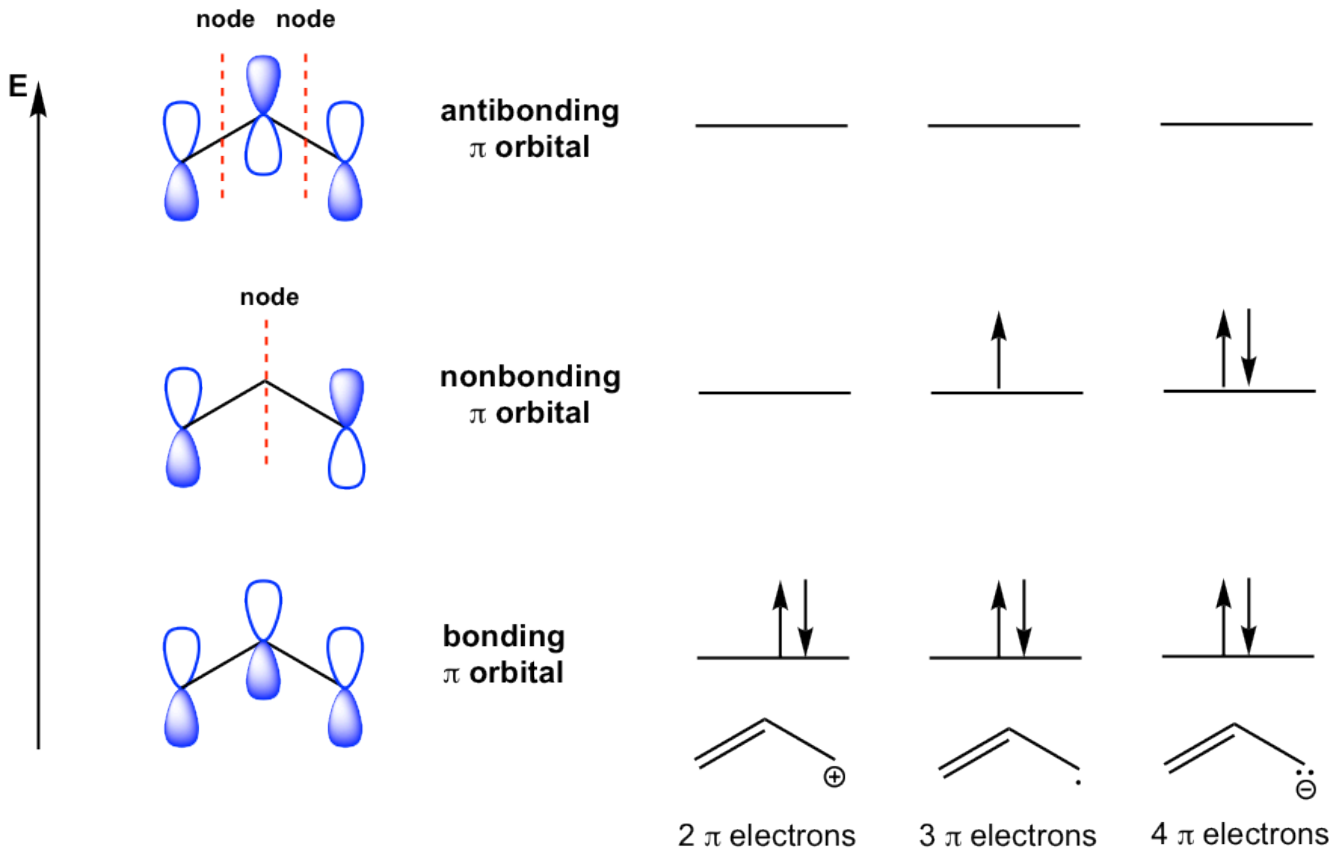


Fig. 3.1d π Molecular orbitals and π electron configurations of allyl species

It is important to know the number of π electrons for each allyl species, which is indicated in the structure of each species. For all the allyl species, the lowest bonding π MO is always filled up with two electrons. The nonbonding MO has none, one or two electrons for different species. However, since there is no electron in the antibonding MO, the energy of each allyl system is lowered overall (and thus stabilized), regardless of cation, radical, or anion.

3.2 Reactions of Allyl System

Radical Halogenation (Substitution) of Allylic Substrates

As mentioned earlier allylic hydrogens are especially reactive in radical halogenation (substitution) reactions. The reaction proceeds through the same mechanism as alkane halogenation that we learned before (refer to **section 9.2 in Book I**). When halogens, Cl_2 or Br_2, are employed for such reactions, however, addition reactions to the double bond readily occur as well. To avoid the competition of addition and promote substitution, high temperature and low concentration of halogens should be maintained to give the allylic halogenation product.

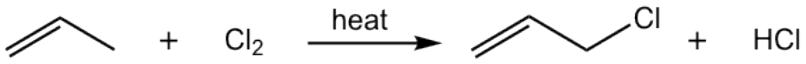


Fig. 3c Radical halogenation of propene

As an alternative to halogen reagents, N-bromosuccinimide (NBS) is the most common reagent applied for allylic bromination.

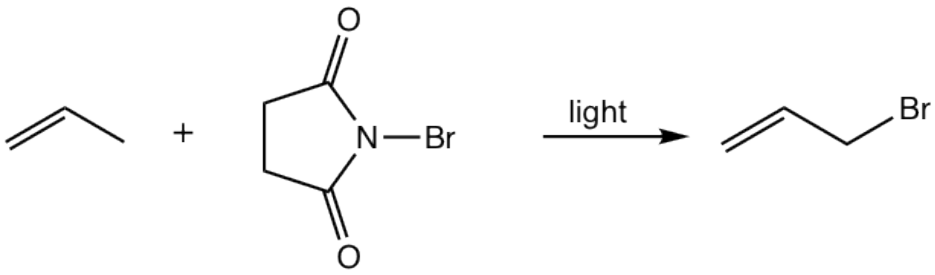


Fig. 3.2a Bromination of propene with NBS

N-bromosuccinimide (NBS) is a solid reagent. By reacting with a trace amount of HBr (usually present in the solvent, such as CCl_4), NBS can provide a constant but **low** concentration of bromine, Br_2. A low concentration of Br_2 facilitates substitution (allylic bromination), and avoids the competition of addition.

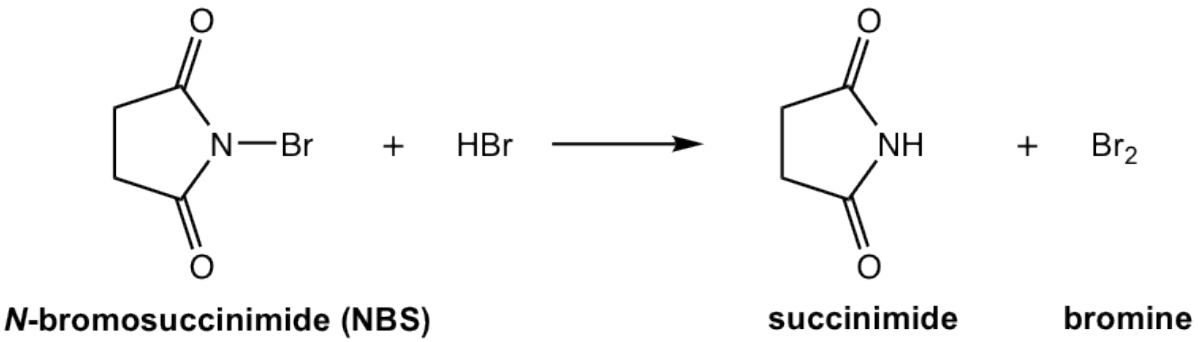
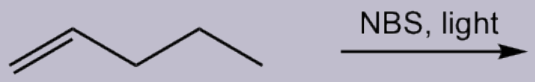


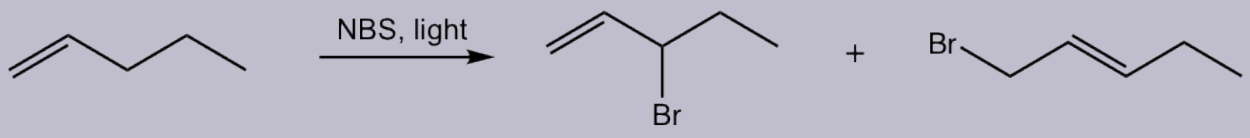
Fig. 3.2b Mechanism for NBS as bromination reagent

Examples

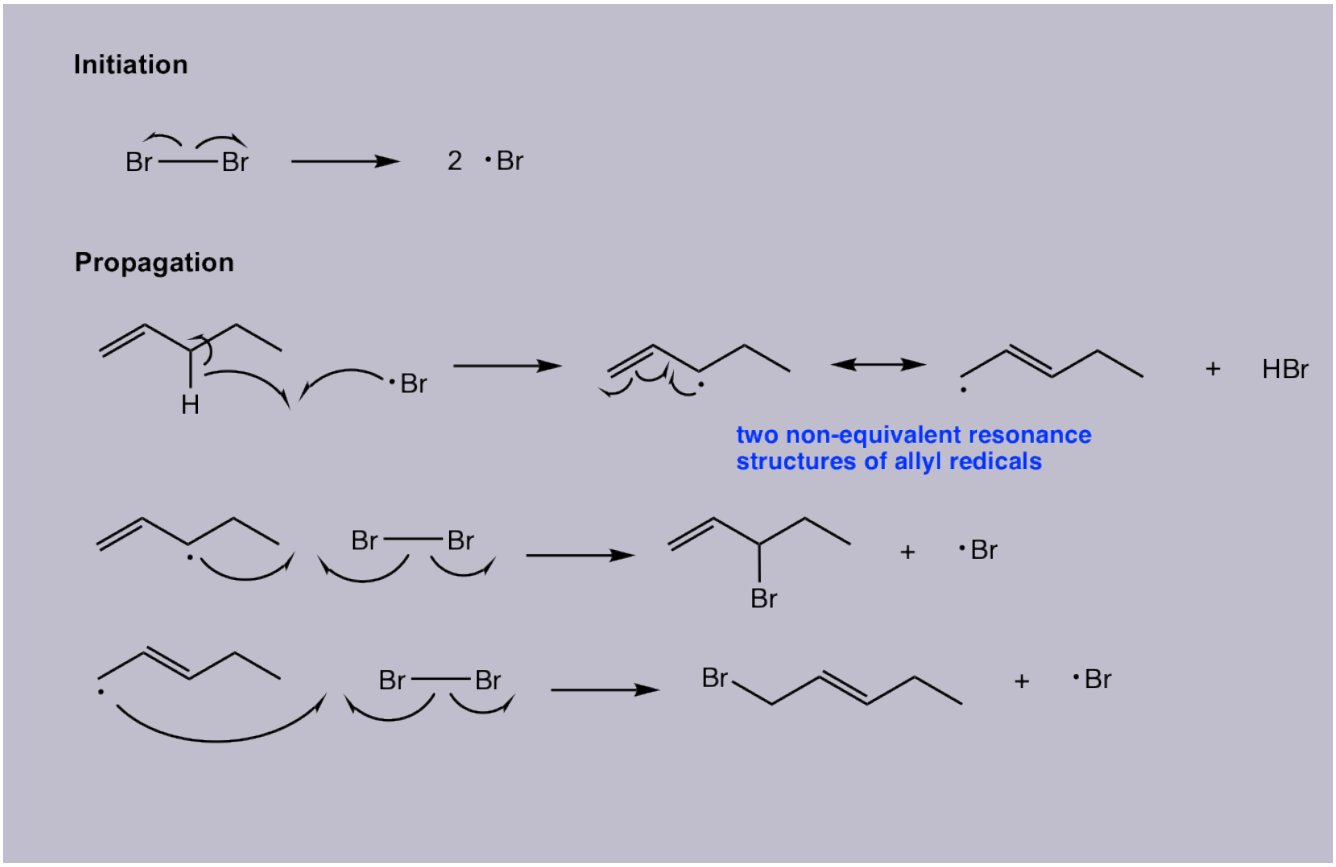
Show the monobromination product of the following reaction.



Answers: A mixture of two constitutional isomers obtained as products.



Analysis: The mechanism explains why. There are two non-equivalent resonance structures for the allyl radical intermediates, each leads to a bromination product.



Nucleophilic Substitution of Allylic Substrates

As the example shown in Fig. 3a, the substrate that forms an allyl carbocation undergoes the S_N1 reaction readily. A few more examples are given in Fig. 3.2c. Multiple products were obtained because of the non-equivalent resonance structures for the allyl carbocation intermediate.

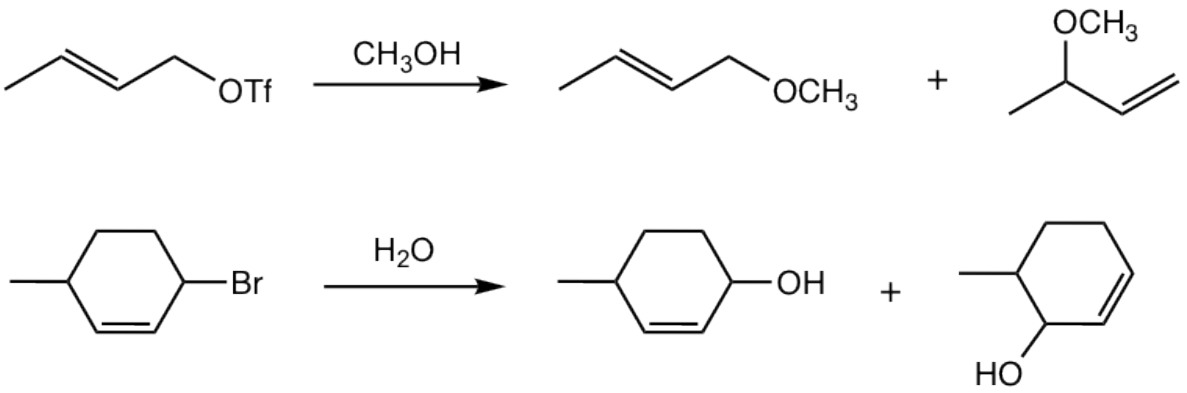


Fig. 3.2c Nucleophilic substitution of allylic substrates

3.3 Conjugated Dienes

Structure and Naming of Dienes

A compound that contains two C=C double bonds is called ***diene***, contains three C=C bonds is called ***triene***. The following examples illustrate IUPAC naming for some simple dienes.

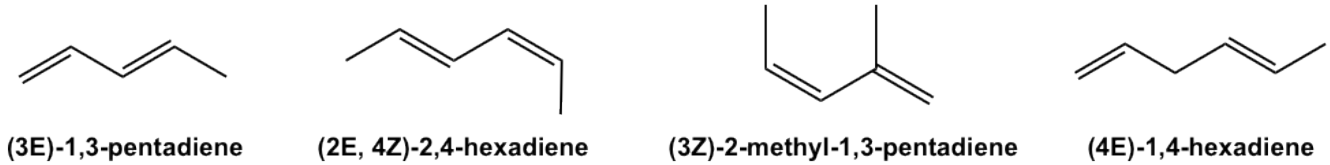


Fig. 3.3a Structures and names of some dienes

The two double bonds can be classified as cumulated, conjugated, or isolated depending on their relative positions.

- Cumulated: the two double bonds share one common carbon.

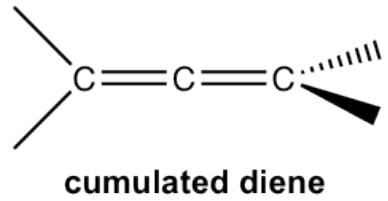


Fig. 3.3b Cumulated diene

- Conjugated: the double bond and single bond alternate along the chain.

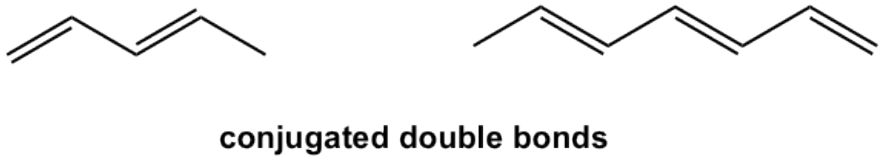


Fig. 3.3c Conjugated dienes

For conjugated diene, there are two possible conformations, the **s-*cis*** and the **s-*trans***. The "cis" or "trans" here indicates the position of the two double bonds are either on the same or opposite side along the single bond in between. These two conformations are interconvertible through the rotation of the single bond for open-chain diene.

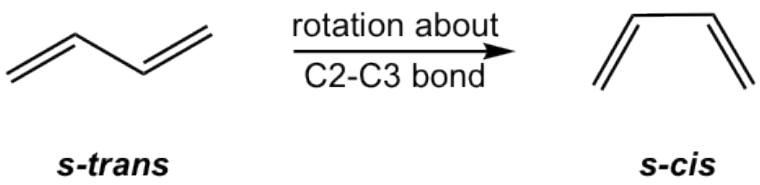


Fig. 3.3d Conformations of conjugated diene

- Isolated: the two double bonds are separated by one or more sp3 carbons in between.

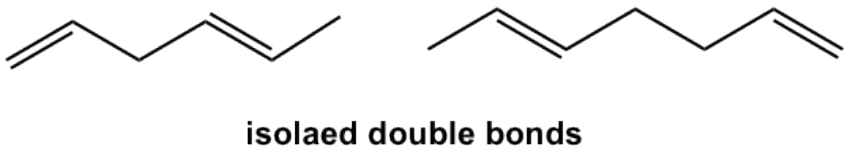


Fig. 3.3e Isolated dienes

Conjugated dienes and conjugated polyenes are also conjugated systems. They will be the topic for this and coming sections, starting from 1,3-butadiene. We will focus on the special chemistry reactivities of these conjugated structures, and understand the reasons behind them.

Stability of 1,3-Butadiene and MO Theory

Similar to the allylic system, 1,3-butadiene also has special stability due to the conjugated structure. One proof of such stability arises from experimental data for the heat of hydrogenation.

The heat of hydrogenation is the heat released when the diene reacts with H_2 gas to produce saturated alkane. The heat of hydrogenation of 1mol of 1,3-butadiene is -239 kJ/mol, and the heat of hydrogenation of 2mol of 1-butene is -254 kJ/mol. The energy difference of 15 kJ/mol is the evidence of stability difference between conjugated diene versus 2 moles of isolated alkenes.

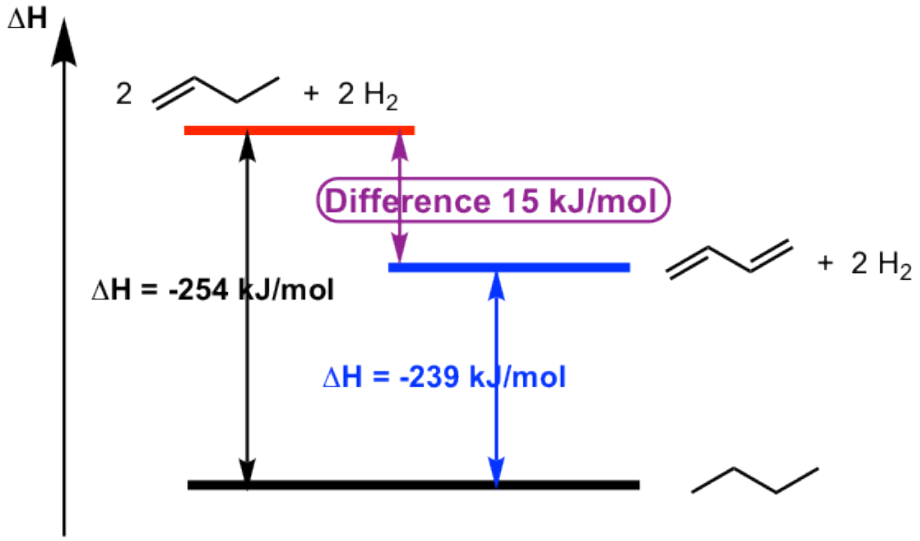


Fig. 3.3f The heat of hydrogenation of 1,3-butadiene and 1-butene

The special stability of conjugated diene can also be explained by molecular orbital theory. All the four carbons in 1,3-butadiene are sp^2 hybridized, each has an unhybridized 2p orbital. The four p orbitals combine to form a set of four π molecular orbitals.

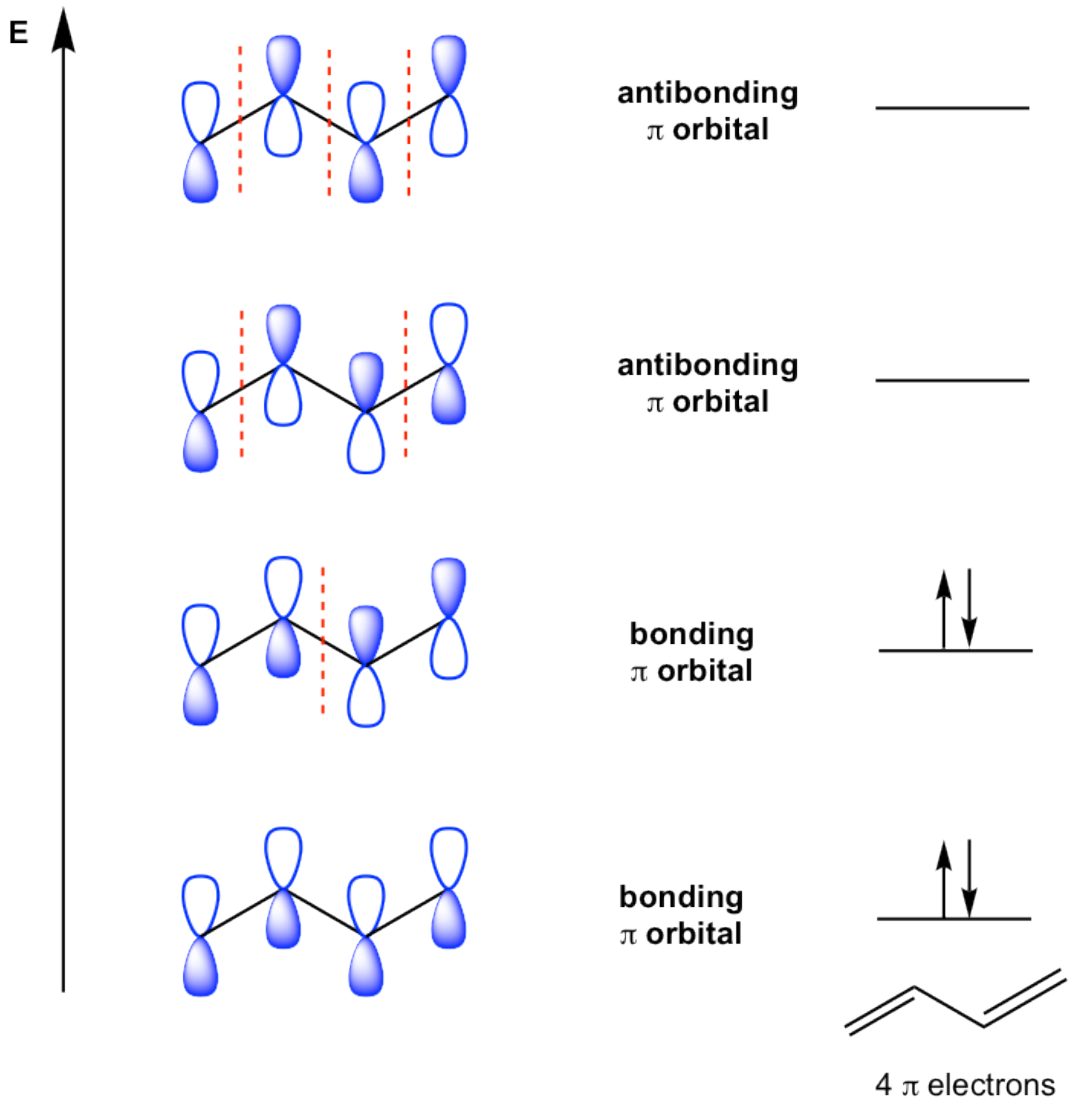


Fig. 3.3g π Molecular orbitals and π electron configurations of 1,3-butadiene

Two of the π molecular orbitals in 1,3-butadiene are bonding MOs, and the other two π molecular orbitals are antibonding MOs. The total four π electrons occupy the bonding orbitals in the ground state of 1,3-butadiene, which explains the special stability of the molecule. Such stability applies to all other conjugated polyenes as well.

3.4 Reactions of 1,3-Butadiene

Electrophilic addition is still the most common and important reaction to conjugated diene, as for other regular alkenes (refer to **section 10.2 in Book I**), however, with a mixture of products produced. The reaction of 1,3-butadiene with HBr is shown in Fig. 3.4a.

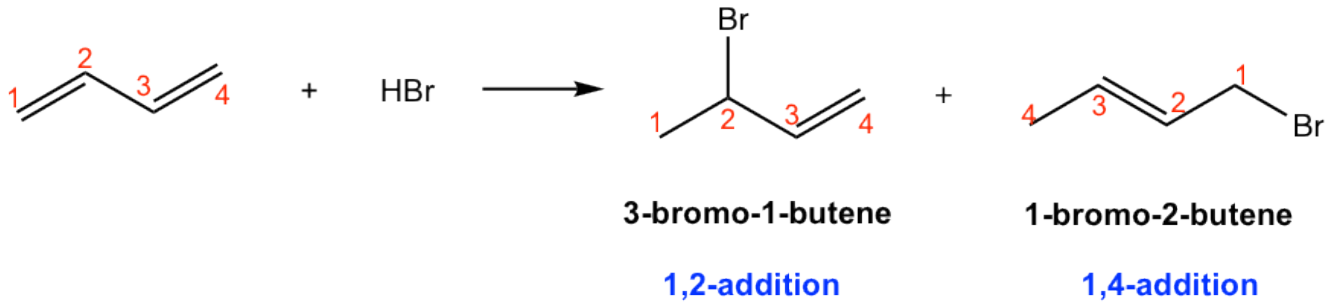


Fig. 3.4a Addition reaction of HBr to 1,3-butadiene

In the first product, 3-bromo-1-butene, small molecule HBr is added to C1 and C2, so the product is called 1,2-addition product. For the addition that produces 1-bromo-2-butene, HBr is added to C1 and C4 positions, and this is called a 1,4-addition product.

The 1,2-addition product is what we would expect, which comes from the addition of HBr to the C=C bond by following Markovnikov's rule. But how about the second product 1-bromo-2-butene? Other than addition, why does the position of the C=C bond move as well? Proposing the reaction mechanism helps to solve the questions.

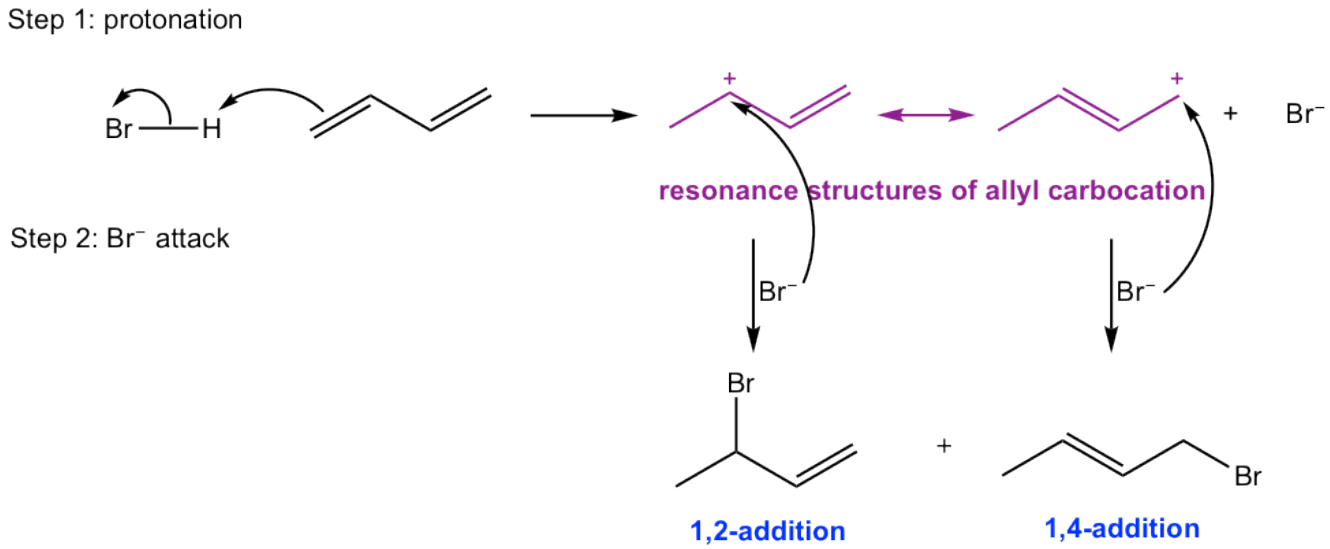


Fig. 3.4b Mechanism for 1,2-addition and 1,4-addition of 1,3-butadiene

The overall mechanism involves two parts: protonation and nucleophilic addition. In the first protonation step, the double bond is protonated by strong acid HBr, and an allyl carbocation intermediate is formed. Because of the special

property for allylic carbonation, as we learned in **section 3.1**, another resonance structure is also available that helps to stabilize the allyl cation. In the second step, the addition of bromide Br- could occur on either of the two allyl carbocations and lead to the formation of two addition products.

As a general trend for electrophilic addition of conjugated diene, a mixture of 1,2- and 1,4-addition products is formed. Further studies indicate that the ratio of 1,2-addition versus 1,4-addition product depends on the reaction temperature. At low temperatures, the 1,2-addition product (kinetic control product) is the major one, while the 1,4-addition product (thermodynamic control product) dominates at high temperatures.

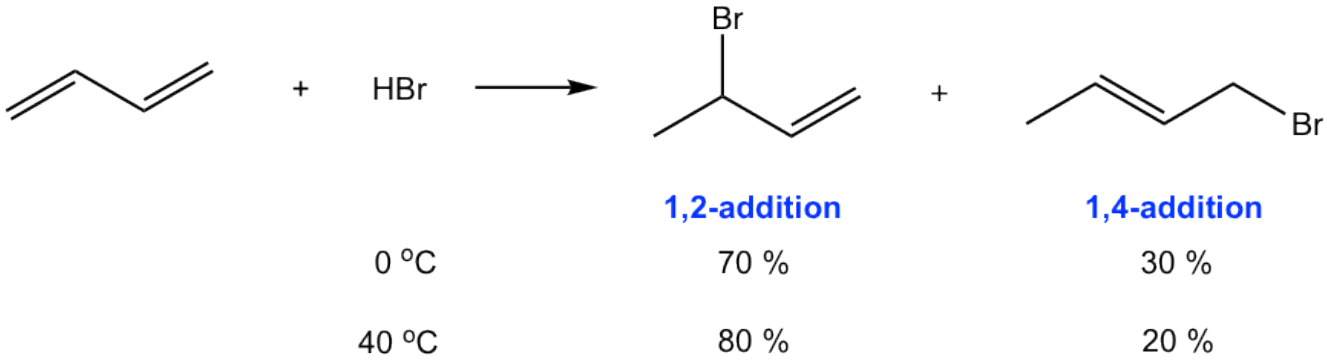


Fig. 3.4c 1,2-addition and 1,4-addition product ratio depends on temperature

Kinetic Control and Thermodynamic Control of Electrophilic Addition to Conjugated Diene

The phenomenon that the amount of 1,2-addition and 1,4-addition product is temperature-dependent, is a great example of an important aspect of reactivity: kinetic control and thermodynamic control.

- **Kinetic control** is the pathway reaction proceeds at low temperature, that is also the path with smaller energy of activation barrier, therefore faster reaction rate (speed).
- **Thermodynamic control** means the reaction proceeds through a pathway that leads to the products with better stabilities (lower energy), and such a pathway has higher activation energy and is favored at high temperatures.

The difference between the two processes is illustrated in the reaction potential energy diagram in Fig. 3.4d. For the addition of 1,3-butadiene, the 1,2-addition product is the kinetic control product (blue pathway) and the 1,4-addition product is the thermodynamic control product (red pathway).

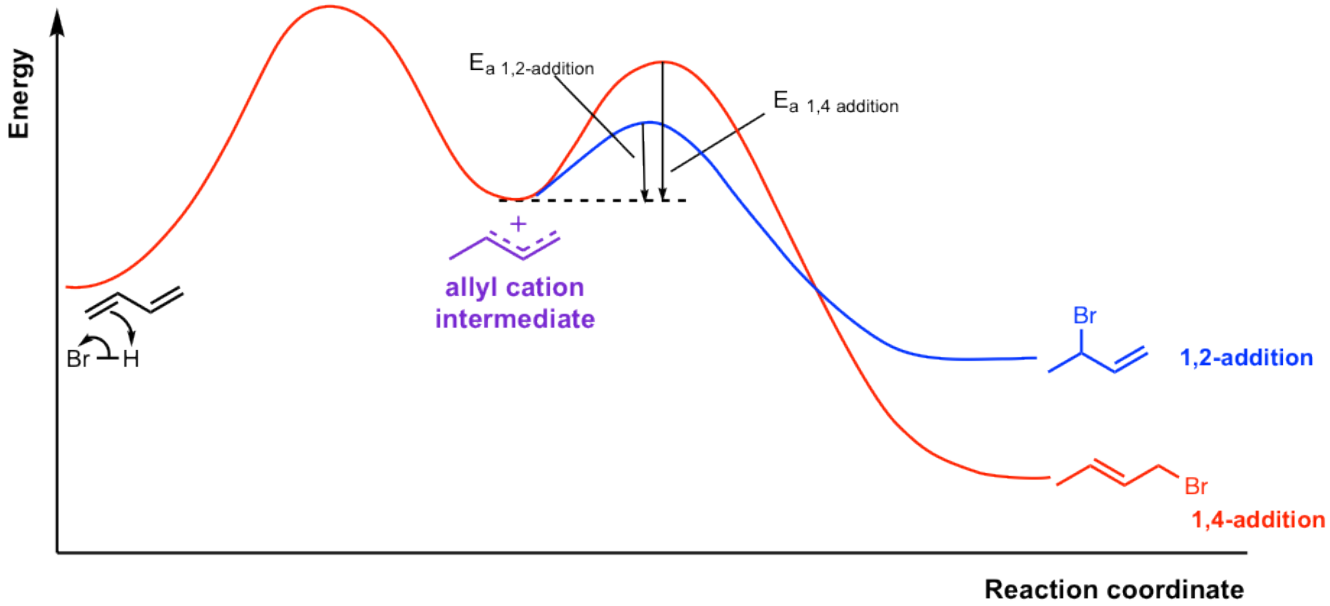


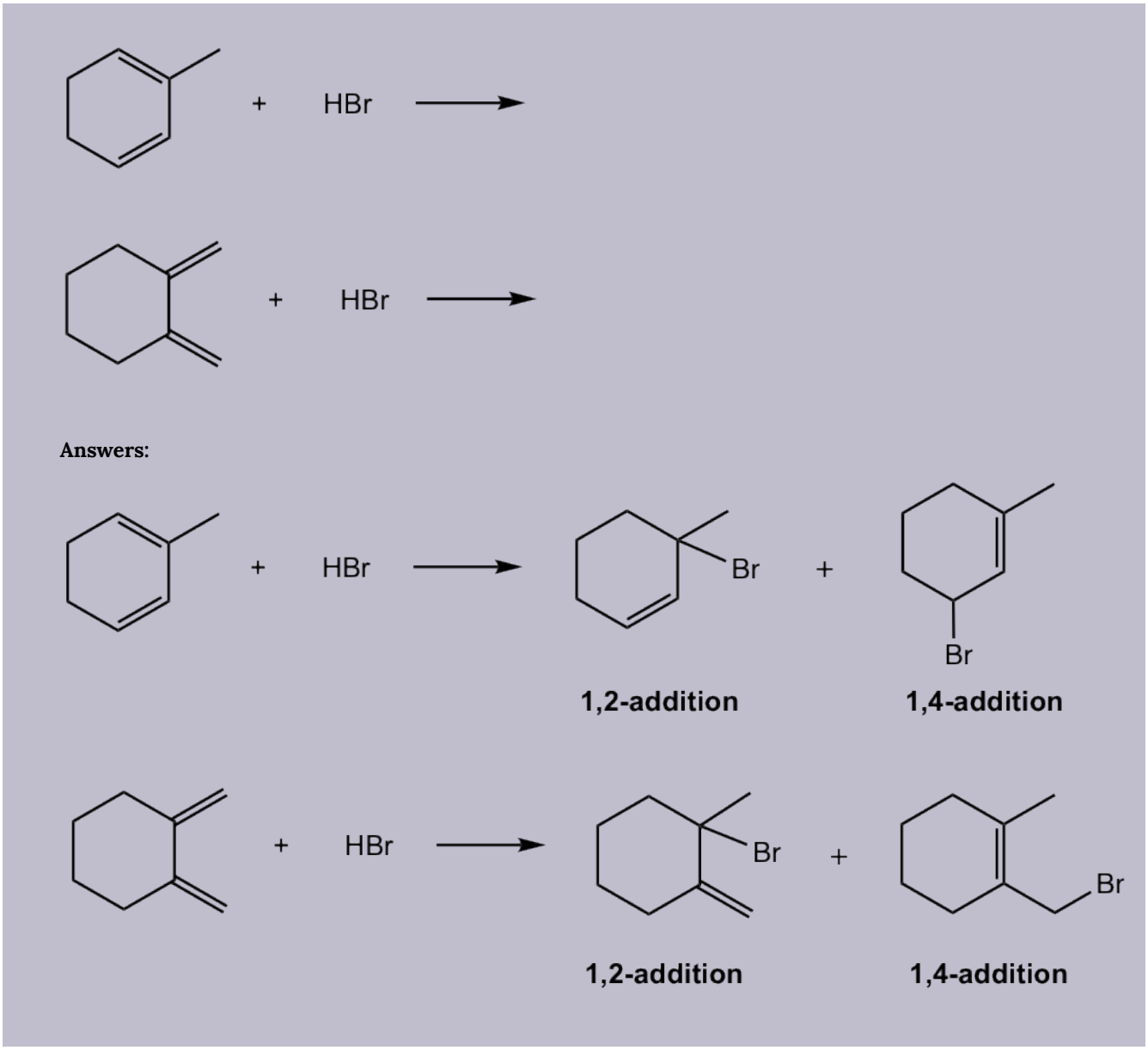
Fig. 3.4d Energy diagram for 1,2-addition and 1,4-addition of HBr of 1,3-butadiene

At low temperatures, there is not enough energy in the reaction system to have enough collisions capable of overcoming the higher energy barrier that leads to the formation of the 1,4-addition product, so the 1,2-addition product predominates because it needs less energy. The formation of 1,2-addition product is faster (low activation energy) and irreversibly at low temperatures.

At high temperatures, there is enough energy to have sufficient collisions that allow the formation of both 1,2- and 1,4-addition products. For such a case, the better stability of the 1,4-addition product (internal alkene with two substituents, lower energy) makes it predominates the equilibrium, and become the major product. Studies also show that when the product mixture from the low temperature (1,2-addition product as major) is warmed up to the higher temperature, the product distribution changes over time with the 1,4-product becoming predominant.

Examples

Show both 1,2- and 1,4- addition products of the following reaction.



Reactions of Polyenes

The electrophilic addition of polyene proceeds in a similar way as for 1,3-butadiene, with the mixture of addition products obtained because of the non-equivalent resonance structures of allyl carbocation intermediates.

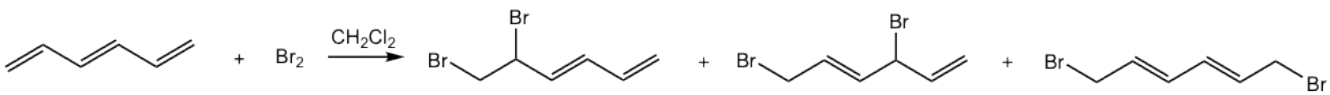


Fig. 3.4e Addition reaction of Br2 to 1,3,5-hexatriene

3.5 Diels-Alder Reaction

A special and superb reaction for conjugated diene is the Diels-Alder reaction, which is also called a 1,4-cycloaddition. In the Diels-Alder reaction, a conjugated diene, simply referred to as the **diene**, reacts with another reactant containing a double or triple bond called the **dienophile** (the species that likes the diene). During the reaction, two new sigma bonds formed that give a six-membered ring, together with a double bond in the ring that comes from the electron pair transfer.

An example of the Diels-Alder Reaction is shown in Fig. 3.5a.

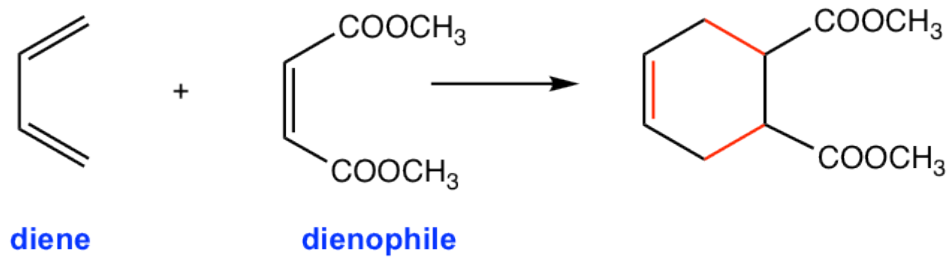


Fig. 3.5a Diels-Alder reaction example

The Diels-Alder reaction offers a great way to build ring structure with great versatility, and has proved to be a synthesis tool with broad applications. Otto Diels and Kurt Alder were awarded the Nobel Prize in 1950 for this brilliant discovery.

3.5.1 Mechanism for Diels-Alder Reaction

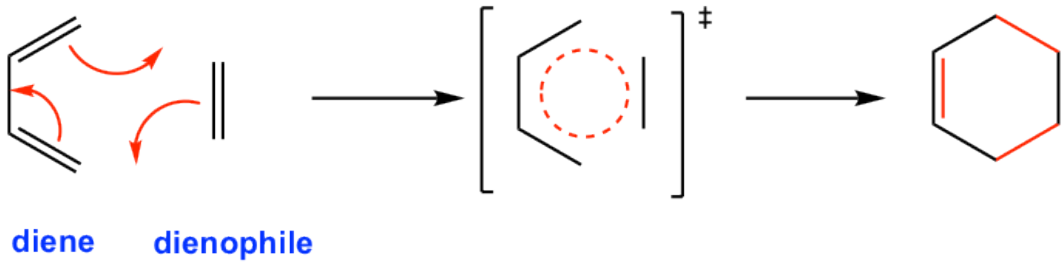


Fig. 3.5b Diels-Alder reaction mechanism

The mechanism for the Diels-Alder reaction (Fig. 3.5b) is a concerted process with all the three π electron pairs transfer taking place at the same time, through a cyclic transition state, to form the six-membered cyclic product. Cycloaddition reactions are classified according to the number of p electrons that interact. Since diene has four p electrons and the dienophile has two p electrons, the Diels-Alder reaction is a [4+2] cycloaddition reaction.

For the Diels-Alder reaction between simplest reactants, for example, 1,3-butadiene reacts and ethene, a high temperature is required and the product is obtained with a low yield. However, the reaction between

2,3-dimethyl-1,3-butadiene and propenal proceeds at 30 °C with an almost quantitative yield of the product, as shown in Fig. 3.5c. Let's see next how the substituents on diene and dienophile affect the rate of the reaction.

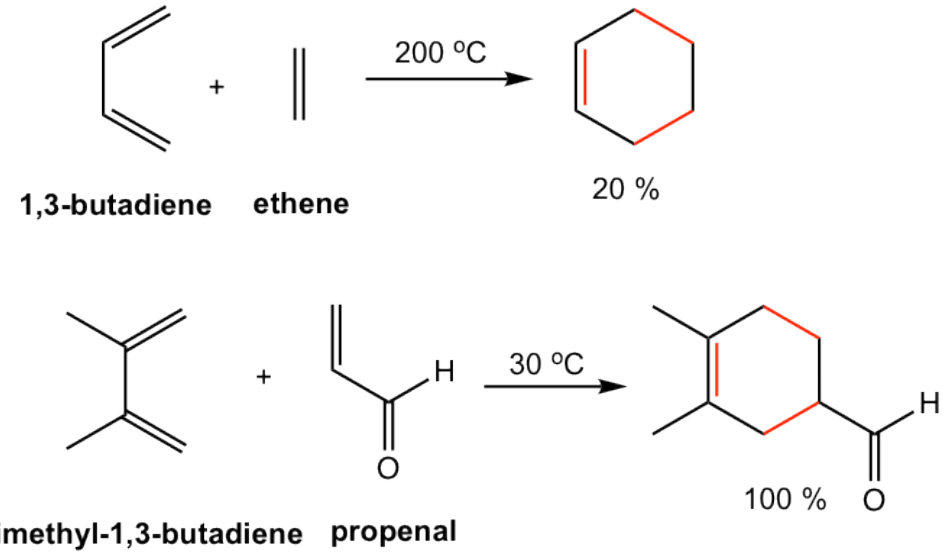


Fig. 3.5c More Diels-Alder reaction examples

3.5.2 Structure Requirements for Diene and Dienophile

The substituents on both reactants have significant impacts on the reaction speed.

> Generally, the ***Diels-Alder reaction is favored by the electron-donating groups in the dienes and the electron-withdrawing groups in the dienophiles***.

Electron-donating groups include alkyl groups and groups that start with the heteroatom which has lone-pair electrons (for example O and N). The electron-withdrawing groups are generally groups with multiple bonds (for example C=O, N=O bonds etc). Examples of EDG and EWG are shown in Fig. 3.5d, more discussions on how to identify EDG and EWG are available in Chapter 5.

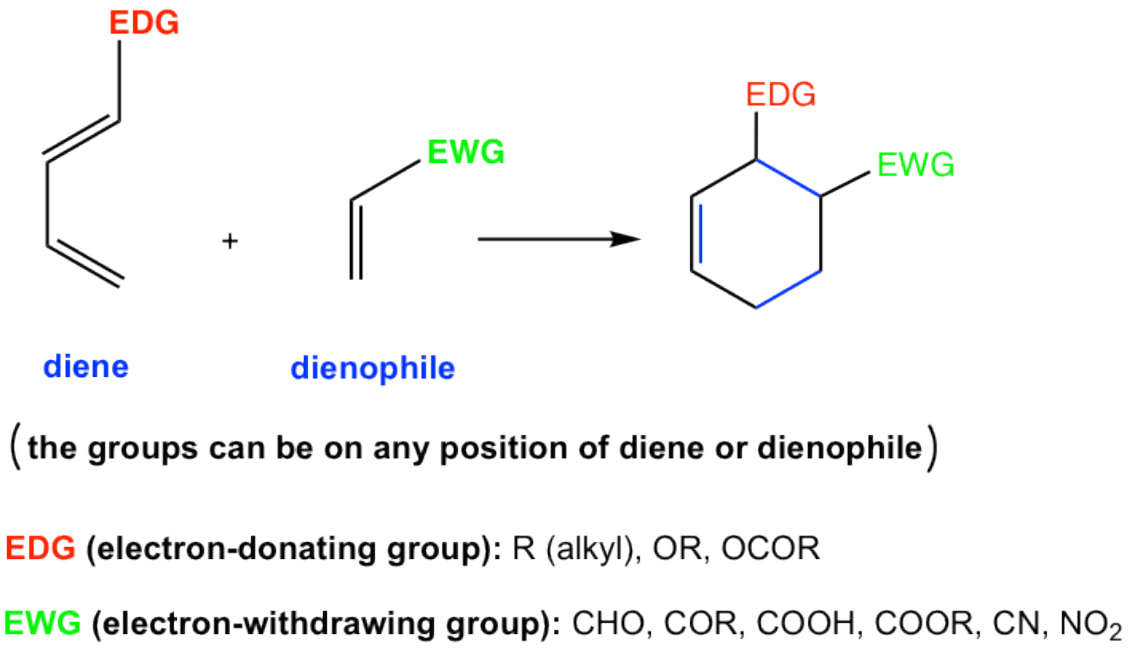


Fig. 3.5d Substituents on dienes and dienophiles that favor the Diels-Alder reaction

Dienes

As mentioned dienes with electron-donating groups are good candidates for Diels-Alder reactions, several examples of such dienes are shown in Fig. 3.5e.

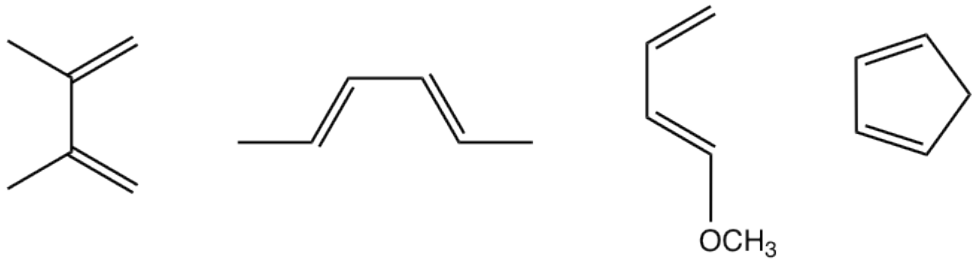


Fig. 3.5e Common dienes with EDG

Since the Diels-Alder reaction is a concerted process, the diene must adopt an s-*cis* conformation for carbon atoms on both ends to bond simultaneously with the dienophile. Although the s-*trans* conformer is more stable for acyclic diene, the two are generally in rapid equilibrium (as shown in Fig. 3.5f), thus allowing the use of most acyclic diene in Diels-Alder reactions.

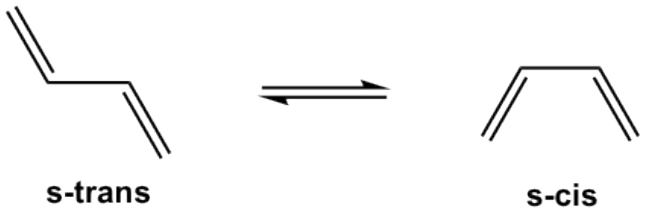


Fig. 3.5f Equilibrium between s-trans and s-cis of acyclic diene

For cyclic dienes in which the double bonds are "locked" in the s-cis conformation, for example, cyclopentadiene, they are especially reactive for the Diels-Alder reaction. The reaction between cyclopentadiene and ethene gives a bicyclic product with a good yield.

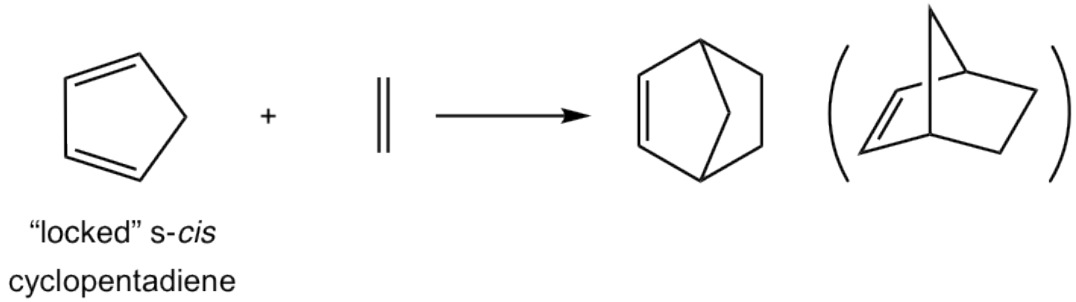
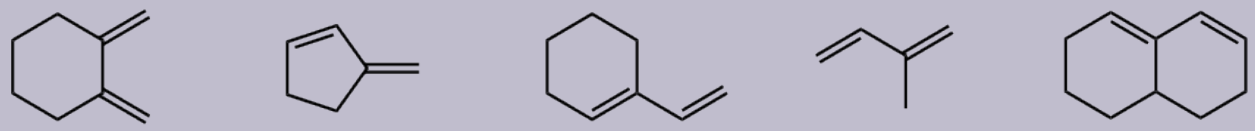


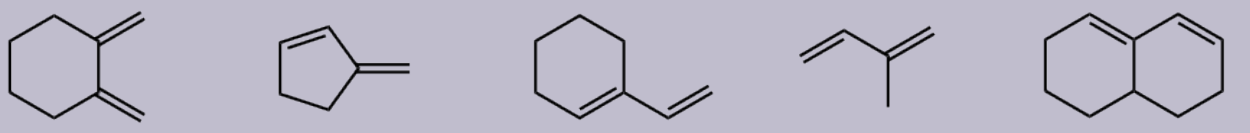
Fig. 3.5g Cyclic diene with locked s-cis conformation in Diels-Alder reaction

Examples

Which of the following dienes **cannot** do the Diels-Alder reaction?



Answers:



Dienophiles

The electron-withdrawing groups on dienophiles speed up the Diels-Alder reaction. Several examples of dienophiles commonly applied are given below.

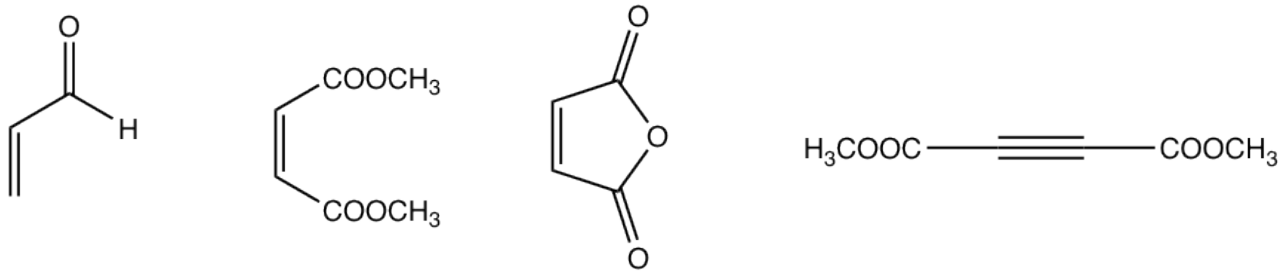
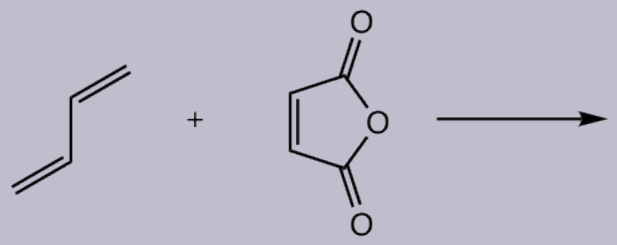


Fig. 3.5h Common dienophiles with EWG

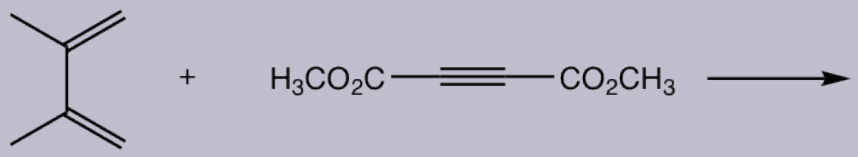
Examples

Show the product of the following Diels-Alder reactions.

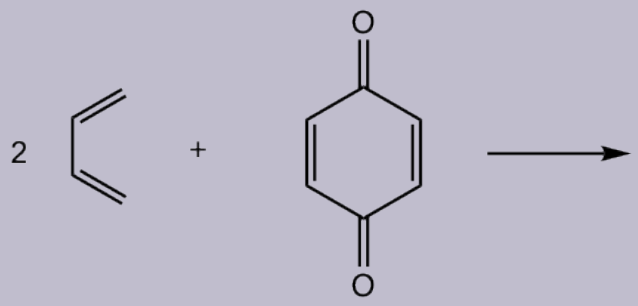
1)



2)



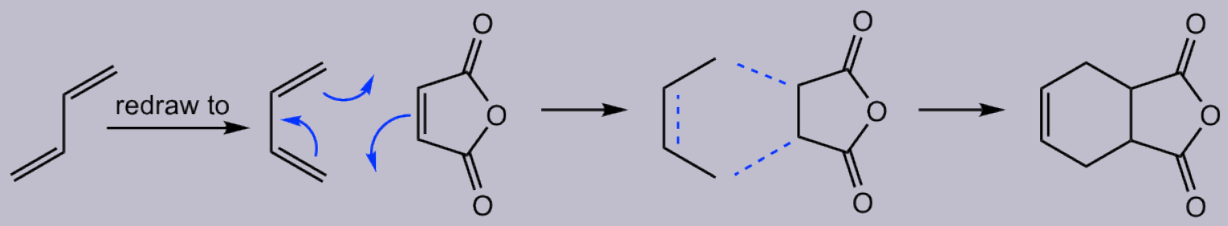
3)



Tips to work out the D-A reaction product: (reaction #1 is shown as example for the process)

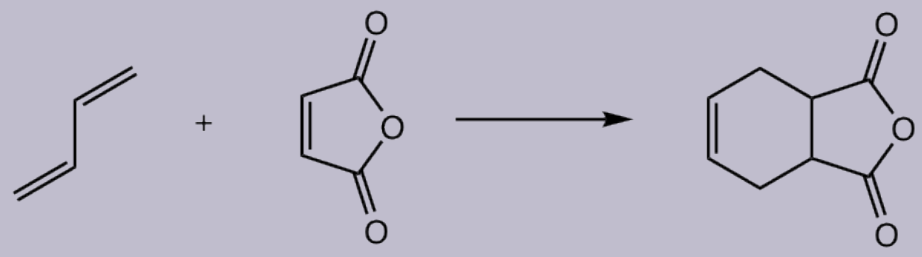
- If the diene is given in s-*trans* conformation, redraw it in s-*cis* conformation.
- Arrange the diene in a way that the carbon atoms at the ends of both double bonds are close to the double bond in the dienophile.
- Connect the atoms, and redraw the bonds: two new σ bonds and one new π bond in the product ring.

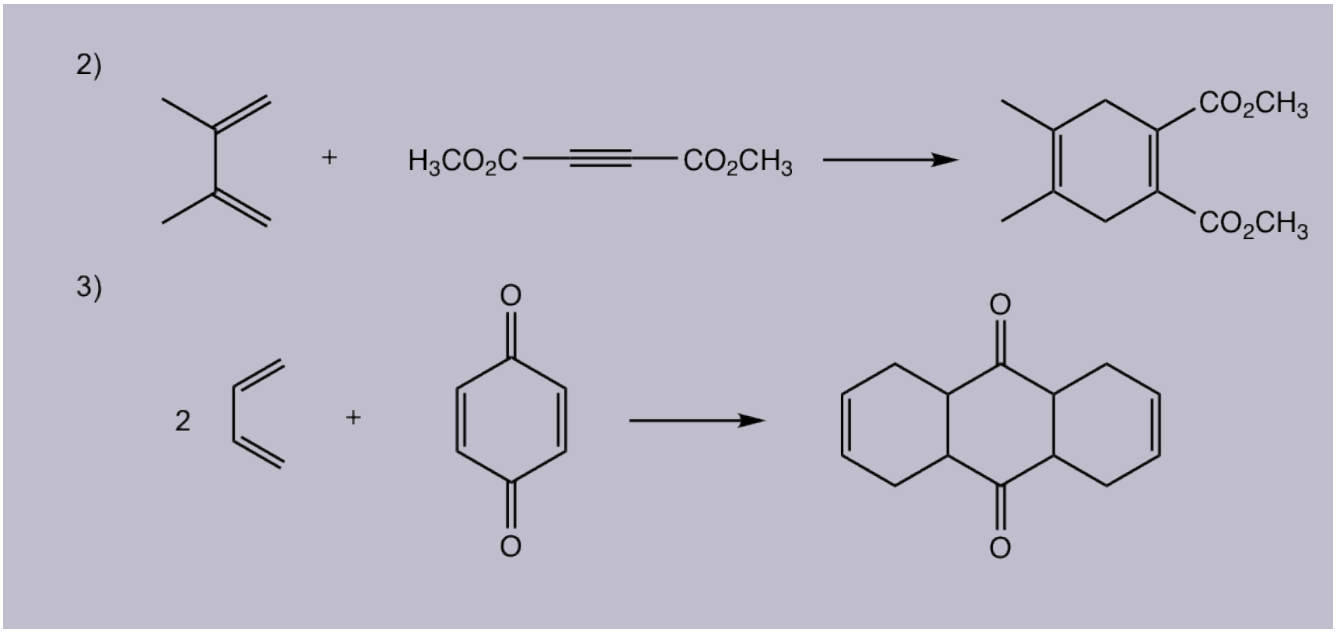
1) "working process" to draw the product



Answers:

1)





3.5.3 Stereochemistry of the Diels-Alder Reaction

Syn addition

As a concerted cyclization process, the Diels-Alder reaction is a **syn** addition, which means one face of the diene adds to one face of the dienophile. As a result, the ***configurations of the diene and dienophile are retained in the product*** (Fig. 3.5i).

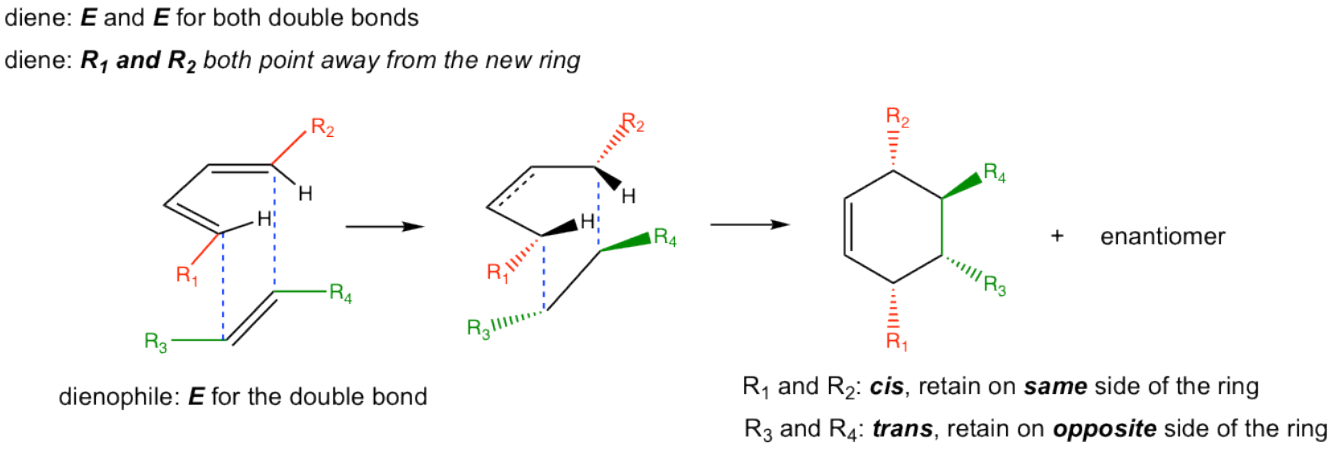


*Fig. 3.5i "**Syn**" addition of Diels-Alder reaction*

— For **dienes**: For dienes that have substituents on C-1 and C-4, the new stereocenters will be formed in the cyclohexene product. The two substituents of diene can be regarded as being either "***cis***" (both facing in or both facing out) or "***trans***" (one facing in and one facing out). The stereochemistry of these substituents in the cyclohexane product is retained as "**cis**" or "***trans***" respectively, as shown in Fig. 3.5j.

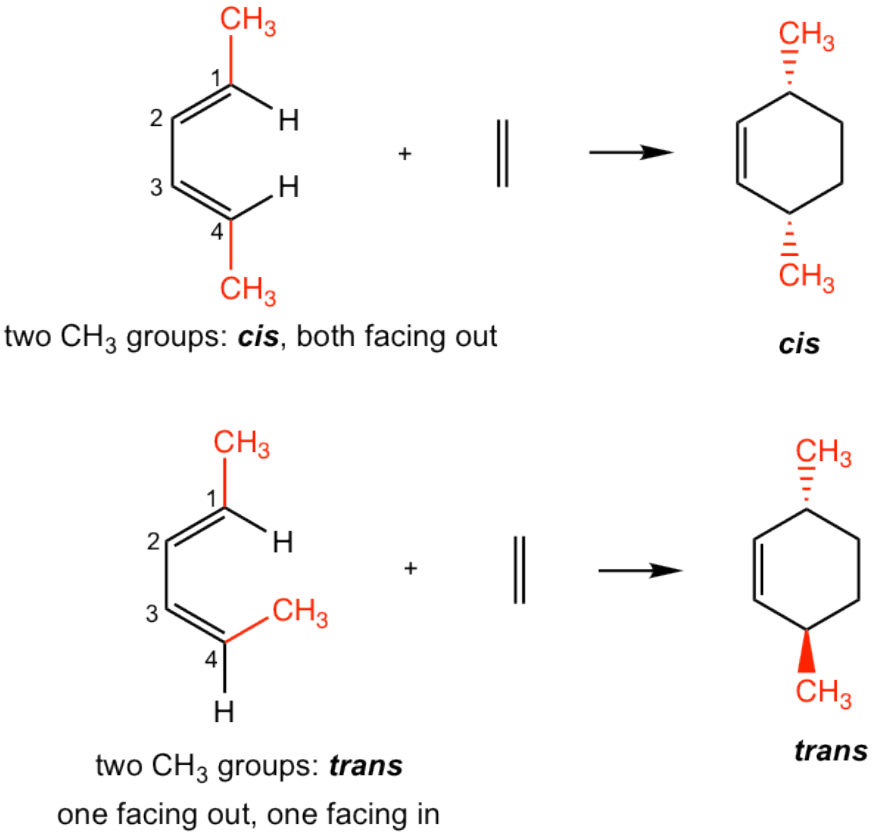


Fig. 3.5j Stereochemistry of dienes for Diels-Alder reaction

— For **dienophiles:** The ***cis*** substituents of the dienophile will retain ***cis*** in the substituted cyclohexane product, and the ***trans*** substituents of the dienophile will retain ***trans*** in the substituted cyclohexane product.

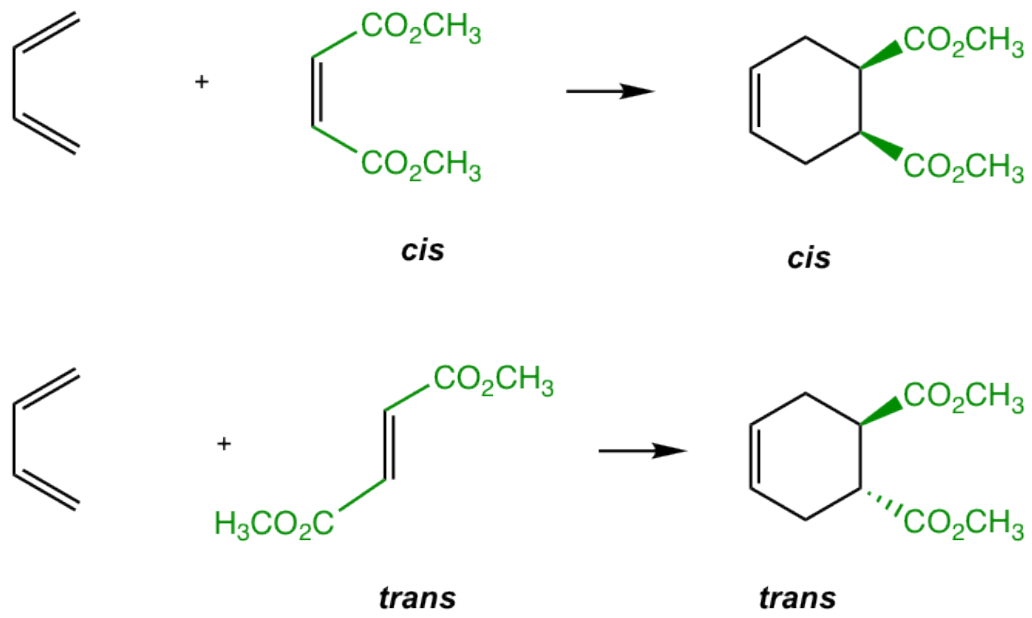
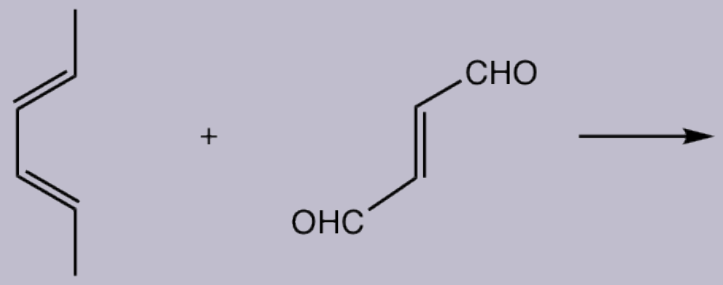
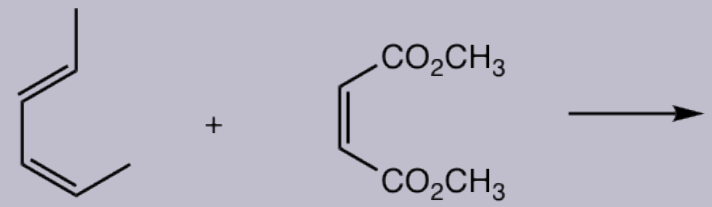


Fig. 3.5k Stereochemistry of dienophiles for Diels-Alder reaction

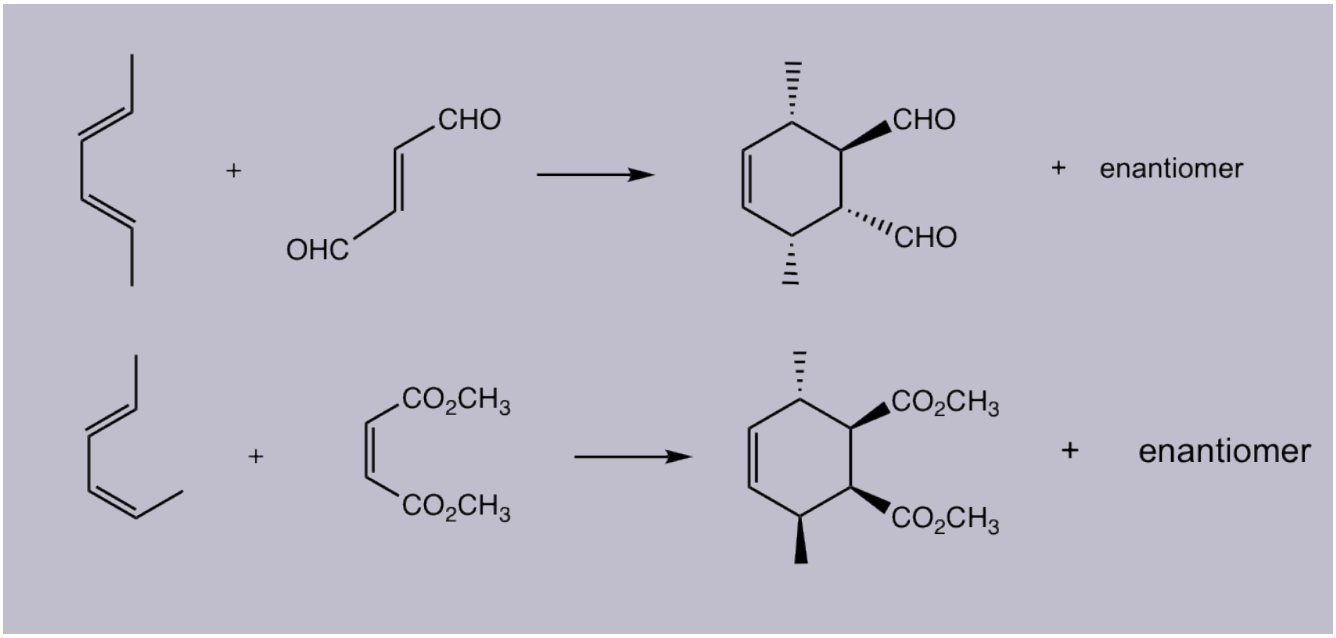
Examples

Show products of the following reactions.





Answers:



Endo Rule

Another stereochemistry characteristic of the Diels-Alder reaction is that ***only the endo product is formed***. The terms *endo* and *exo* are used to indicate the orientation of substituents in a bicyclic ring system. The ***endo*** position on a bicyclic structure refers to the position that is closer (or *inside*) to the concave shape of the larger (six-membered) ring, and the ***exo*** position is away from (or *outside*) the larger ring as shown in Fig 3.5l.

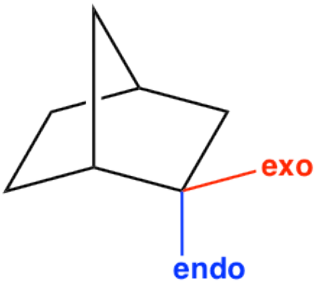


Fig. 3.5l ***Endo*** *and* ***exo*** *position*

In the Diels-Alder reaction, ***endo*** or ***exo*** refers to the orientation of the dienophile when it reacts with diene. A good dienophile, as mentioned earlier, always has an e-withdrawing group, such as a carbonyl-containing group. When the π electron orbitals in the carbonyl group align under (or above) the π electron orbitals on the diene, the orientation of the approach is called ***endo***, as shown in Fig. 3.5m. The ***endo*** approach allows the orbital overlapping of the carbonyl group with the diene, and lowers the energy of the transition state, therefore is the favorable way of the reaction.

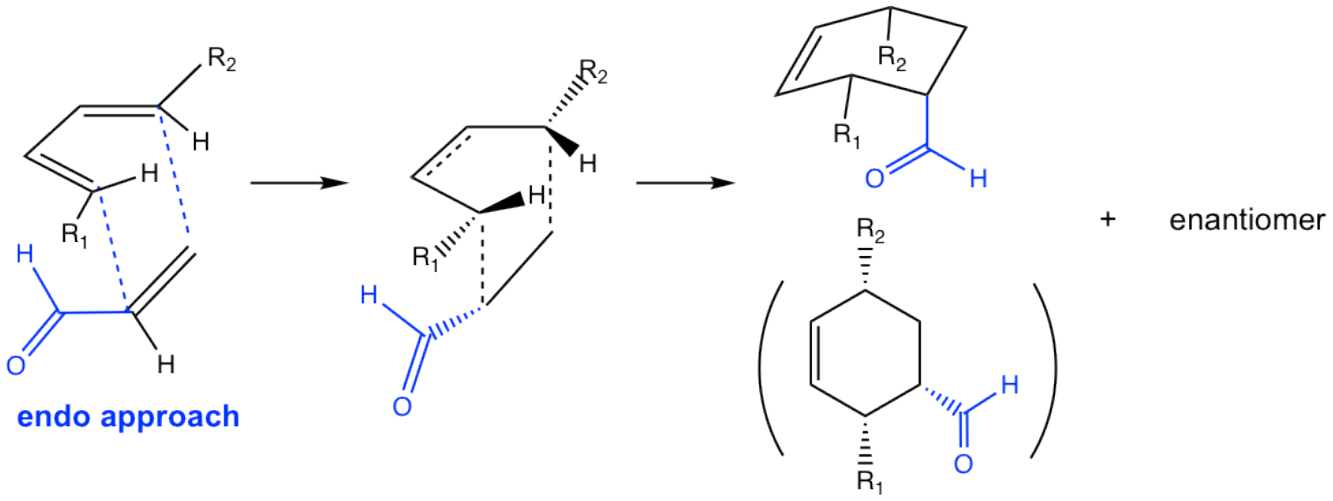


*Fig. 3.5m Diels-Alder reaction in **endo** approach*

If the reaction proceeds in the ***exo*** approach, on the other hand, the π electron orbitals in the carbonyl group align away from the π electron orbitals on the diene.

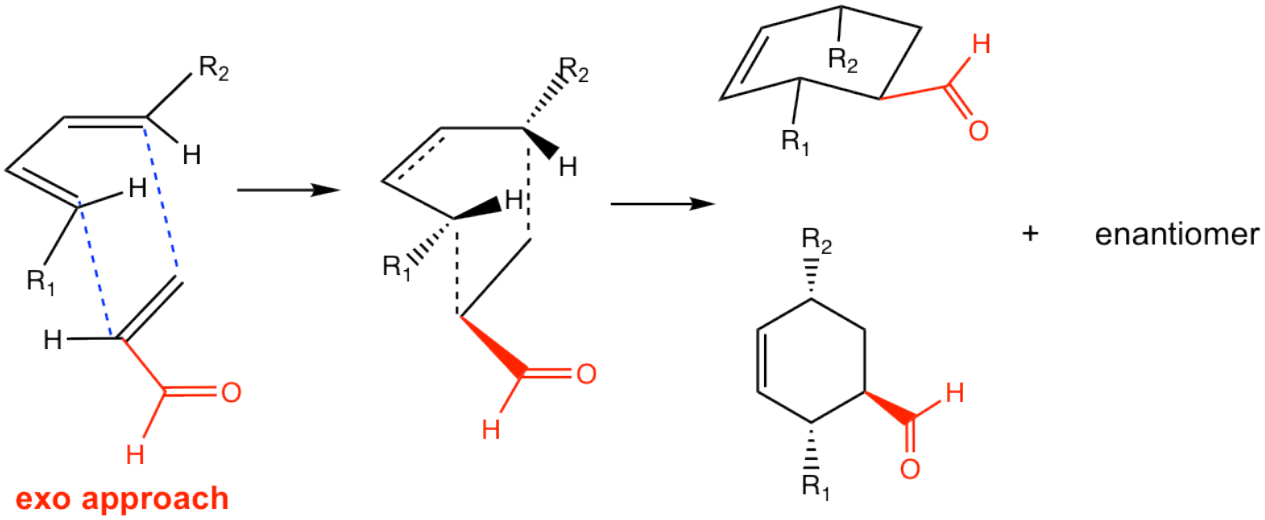
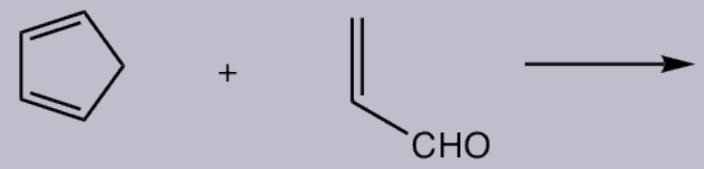
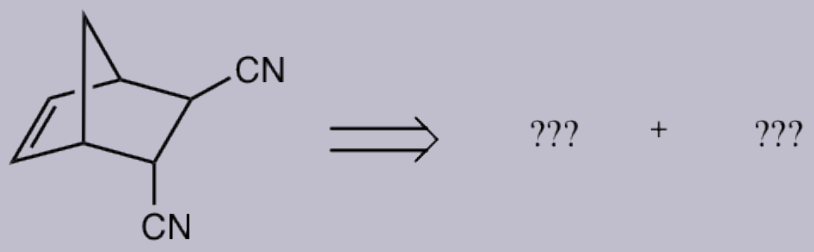


*Fig. 3.5n Diels-Alder reaction in **exo** approach (hypothetic situation)*

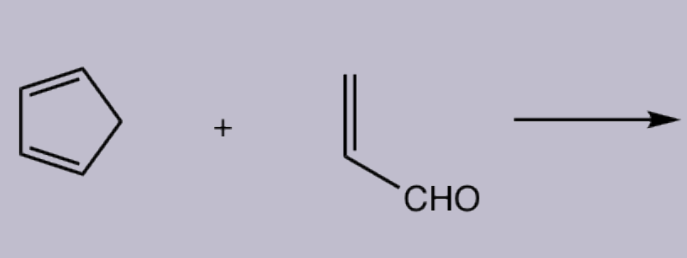
Examples

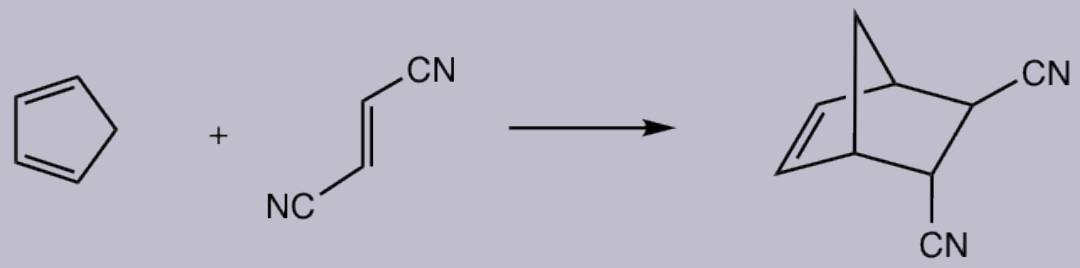
Show the product or the reactants of the following reactions.





Answers:

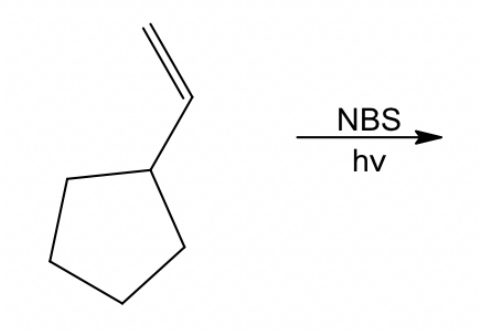




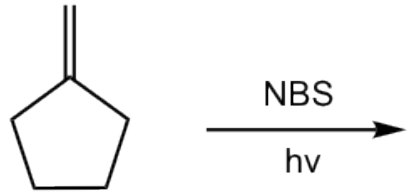
3.6 Practices

Show the major product(s) of the following reactions.

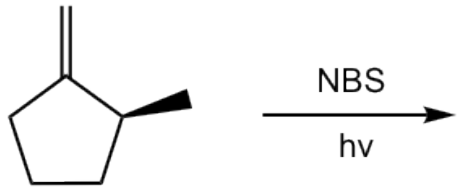
a.



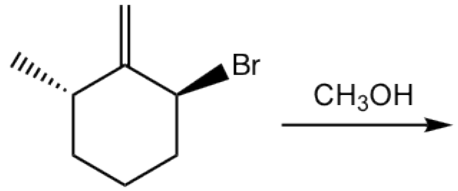
b.



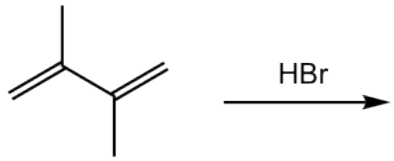
c.



d.

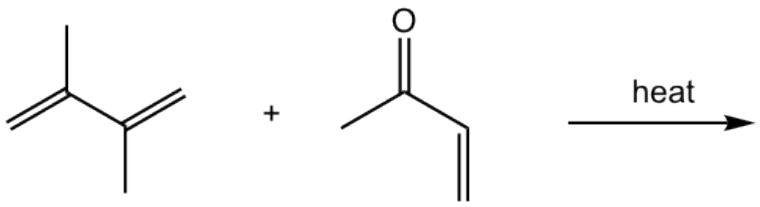


e.



f.

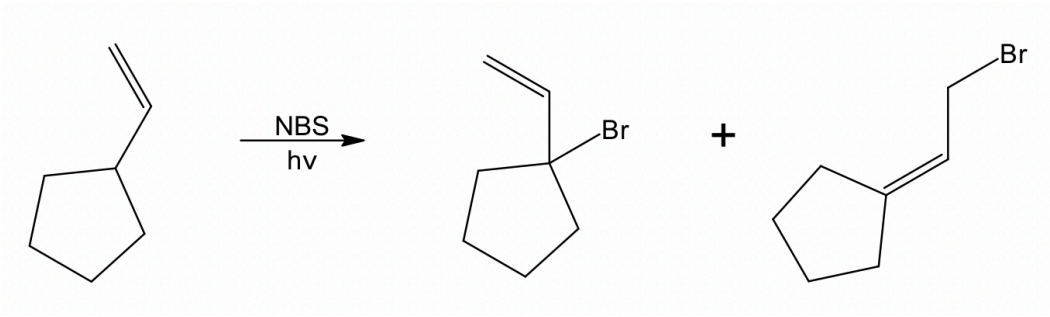
g.


O
+
heat

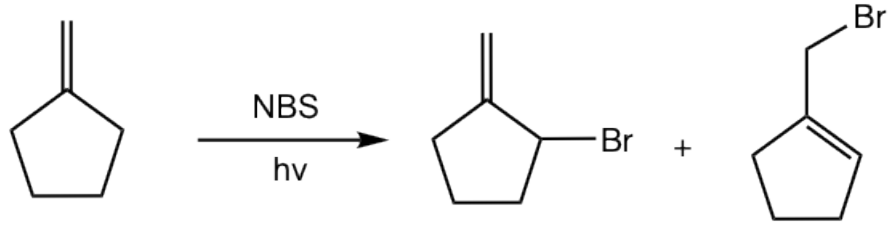
3.7 Practices Answers

Show the major product(s) of the following reactions.

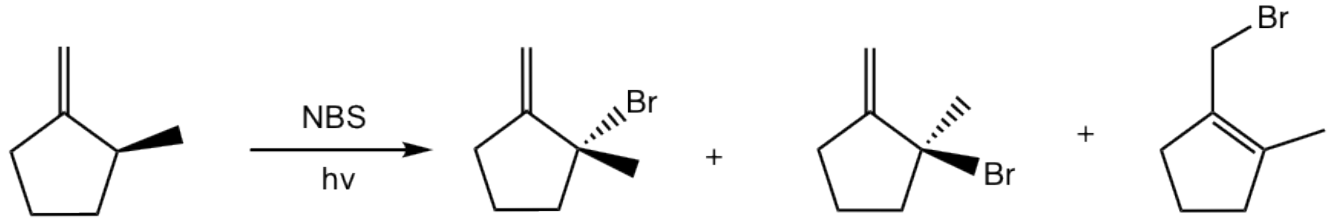
a.



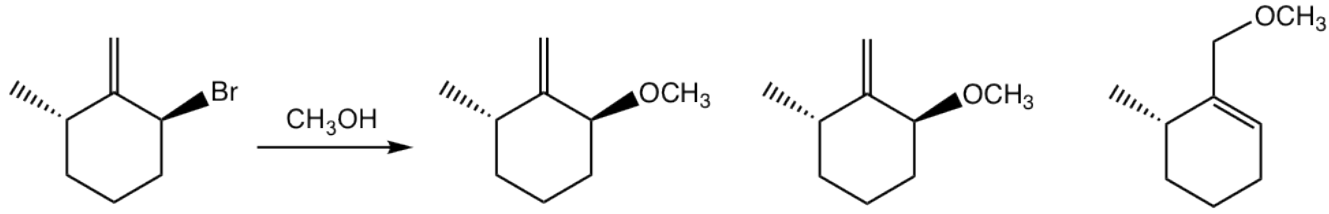
b.



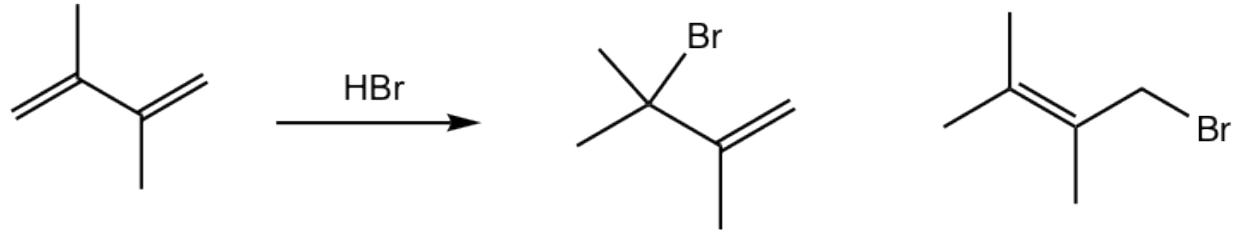
c.



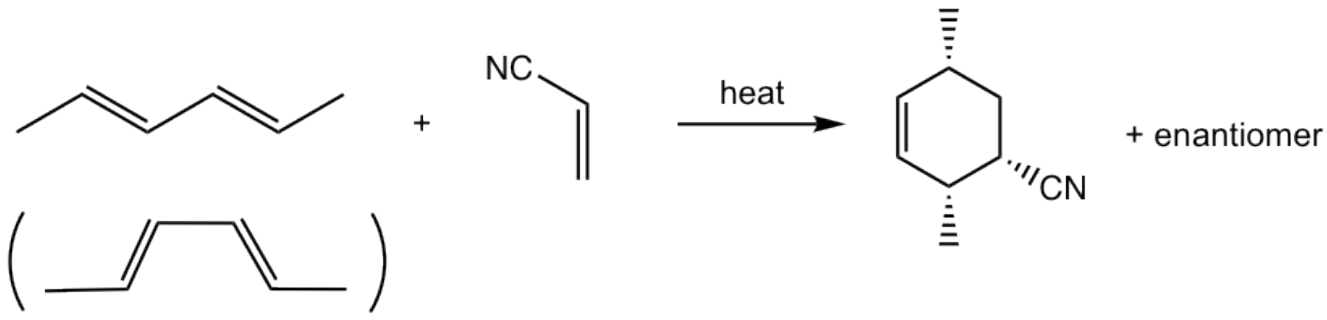
d.



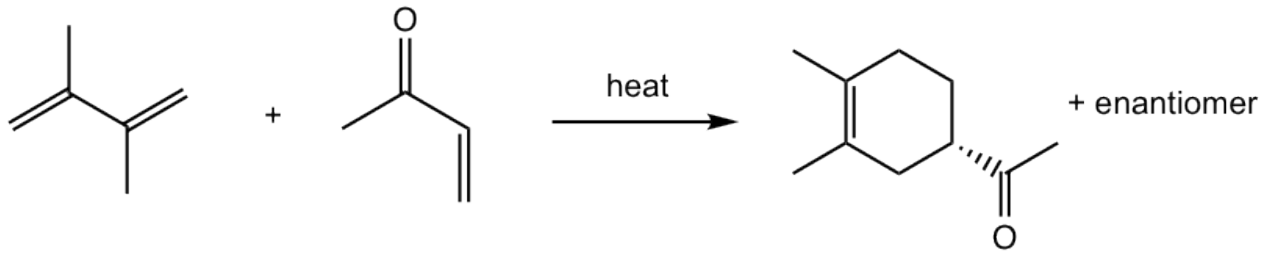
e.



f.



g.



CHAPTER 4: AROMATIC COMPOUNDS

The word “aromatic” refers to the pleasant odour from some resources, such as flowers, trees, cinnamon buns, etc. In the early history of organic chemistry, it was found that a group of compounds usually isolated from natural resources, such as oil, and plants, have such a pleasing sweet smell, and they all have the structure unit of the benzene ring. The word “aromatic compound” was used for such a group of compounds containing benzene rings. The meaning of “aromatic” in contemporary organic chemistry, however, has been further extended to compounds that have benzene rings, fused benzene rings, or cyclic structures that have similar properties as benzene. The pleasant smell is not the necessary common feature for aromatic compounds anymore, instead, they all share similar chemical stability and reactivity because of their unique electronic structure features.

The benzene ring is still the most characteristic structure for aromatic compounds. It can usually be represented in different ways.

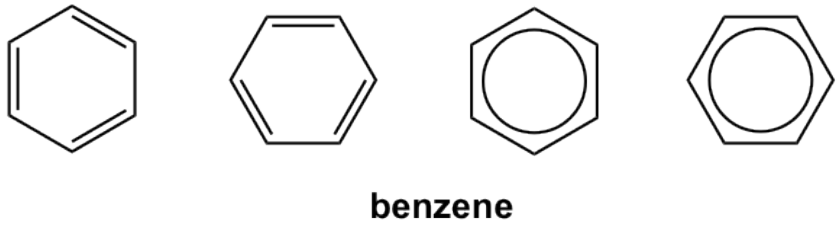


Fig. 4a Different ways to draw the benzene ring

We will start with the properties of benzene and derivatives, and then introduce aromatic compounds with other cyclic structures.

4.1 Naming of Benzene and Benzene Derivatives

The naming of benzene and simple benzene derivatives has been included in **section 2.4 in Book I**. Several highlights and more examples are given here.

- In simple compounds, ***benzene*** is the parent name.
- For some substituted benzenes, the substituent and the ring are taken together and the common names are used broadly.

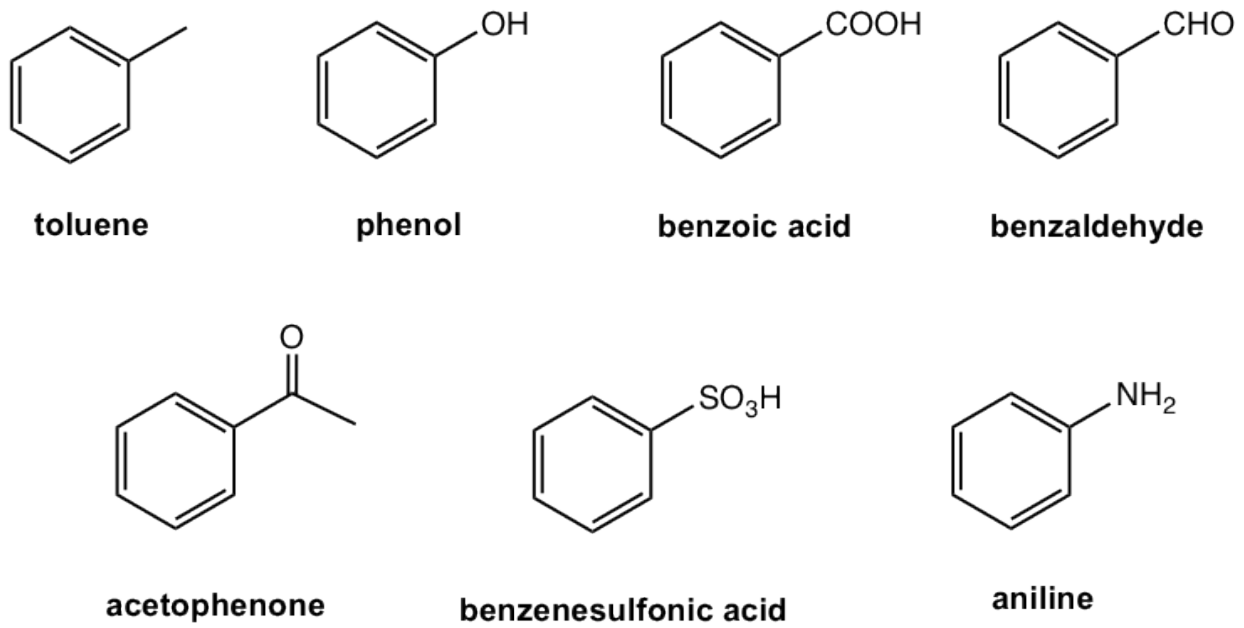
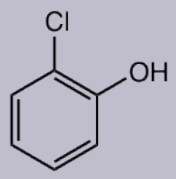


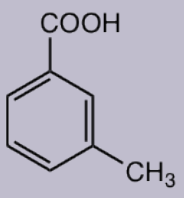
Fig. 4.1a Common names of some substituted benzenes

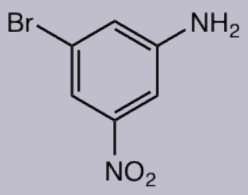
- For disubstituted benzene, the prefixes ortho- (*o*-), meta- (*m*-), and para- (*p*-) could be used for 1,2-, 1,3- and 1,4- respectively.
- When the benzene ring is regarded as a substituent, it is called a ***phenyl*** group.

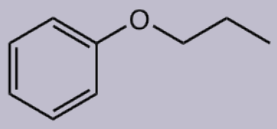
Examples

Name the following compounds.

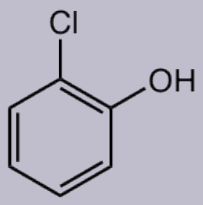




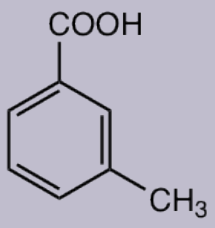




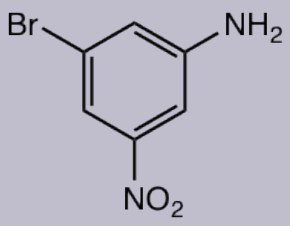
Answers:



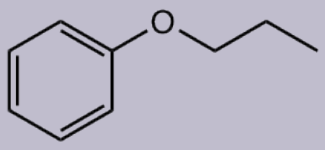
2-chloro-phenol
(o-chloro-phenol)



3-methyl-benzoic acid
(o-methyl-benzoic acid)



3-bromo-5-nitroaniline



phenyl propyl ether

4.2 Reactivity, Stability and Structure of Benzene

Even though the benzene ring was represented as a hexagon ring with alternating doubles and single bonds, the property and reactivity of benzene have nothing to do with usual alkenes (double bonds). Instead, the benzene ring shows special reactivity and stability.

First, the most common reaction of benzene is substitution, instead of the addition reaction for alkenes.

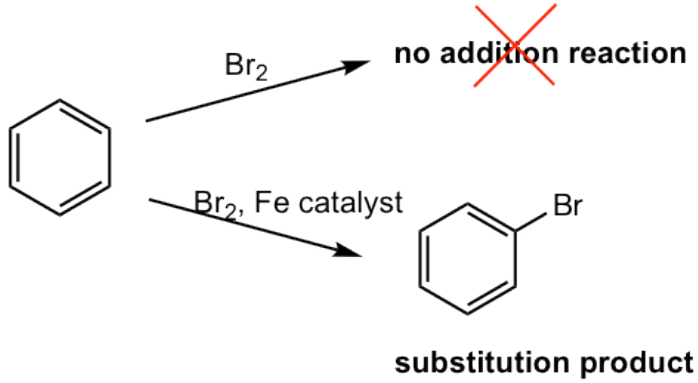


Fig. 4.2a Benzene undergoes substitution instead of addition

Secondly, the heat of hydrogenation data indicates the unique thermostability of the benzene ring. The heat of hydrogenation for cyclohexene with 1mol of hydrogen to cyclohexane is -120 kJ/mol, and that of 1,3-cyclohexadiene with two equivalents of hydrogens is -232 kJ/mol. The ΔH of the cyclohexadiene is roughly twice that of cyclohexene, with 8 kJ/mol less. The difference can be explained due to the stability of conjugated diene, as we learned in **section 3.3**.

According to the above trend, the calculated ΔH of benzene (if benzene does behave as "cyclohexatriene") should be about -360kJ/mol. However the actual amount is -208 kJ/mol, way less than the calculated value, and it indicates that ***benzene is much more stable*** than cyclohexatriene. Such an energy difference of 152 kJ/mol indicates that the benzene ring is much more stable than a "regular" conjugated system. The special stability of benzene can be explained in two ways: resonance theory and molecular orbital theory.

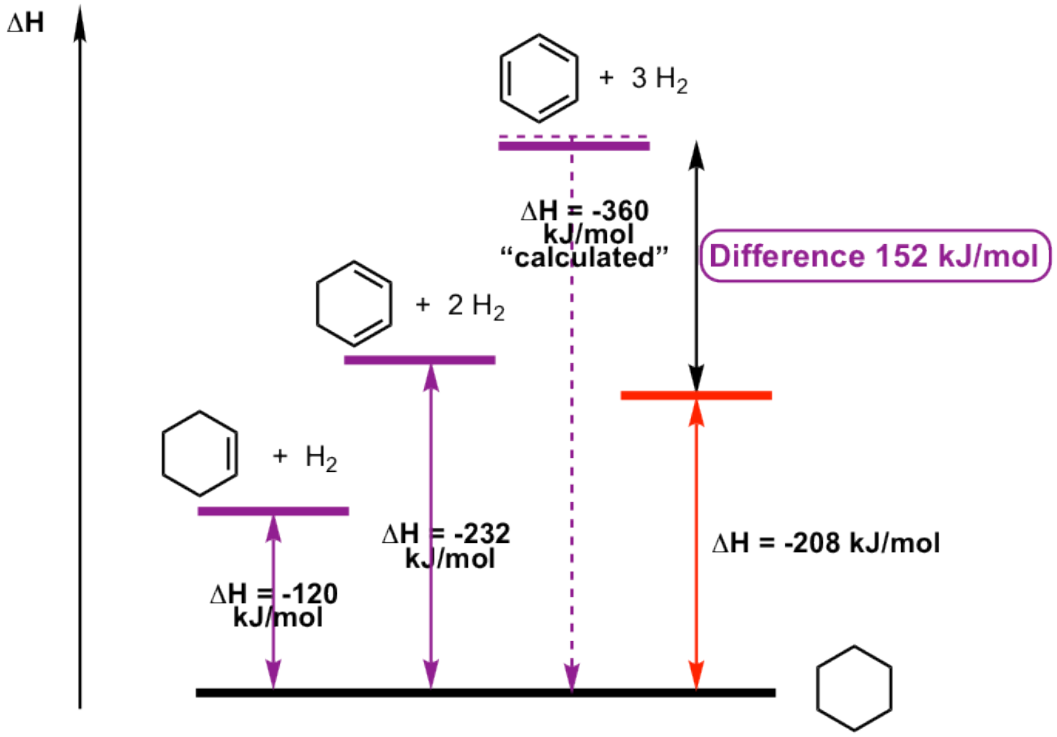


Fig. 4.2b Heat of hydrogenation of benzene vs cyclohexene, 1,3-cyclohexadiene and 1,3,5-cyclohexatriene (hypothetical)

Resonance Structures of Benzene

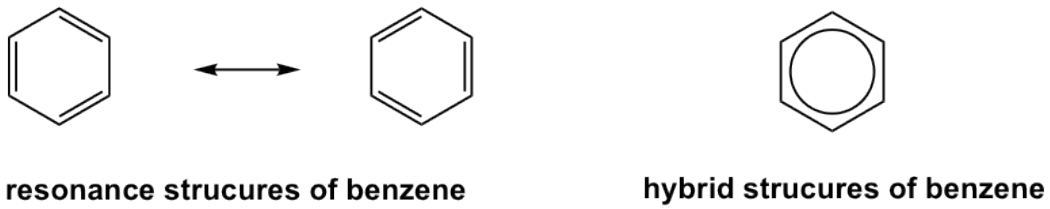


Fig. 4.2c Resonance structures of benzene

According to resonance theory, there are two equivalent resonance contributors for the structure of benzene. A hybrid structure (represented by a circle inside the hexagon) that has neither pure sing bonds nor pure double bonds represents the actual structure of benzene in a better way. Further experiment evidence shows that all of the carbon-carbon bonds in benzene are of the same length, so they are all the same type of bond with the same bond order, and they are neither pure single bonds nor pure double bonds. All the bond angles in the benzene ring are 120°, therefore all the carbons are in sp^2 hybridization with an unhybridized 2p orbital for each. The six carbon atoms construct a planar ring, and all the 2p orbitals are parallel to each other. Rather than form three localized π bonds, the six 2p orbitals overlap all together and form a ***big delocalized π bond***, which explains the unique stability of the benzene ring. The

energy difference of 152 kJ/mol between benzene and hypothetical 1,3,5-cyclohexatriene therefore can be called the resonance stabilization energy.

The molecular orbital theory then applies to understanding more about the delocalized π bond.

Molecular Orbital Theory

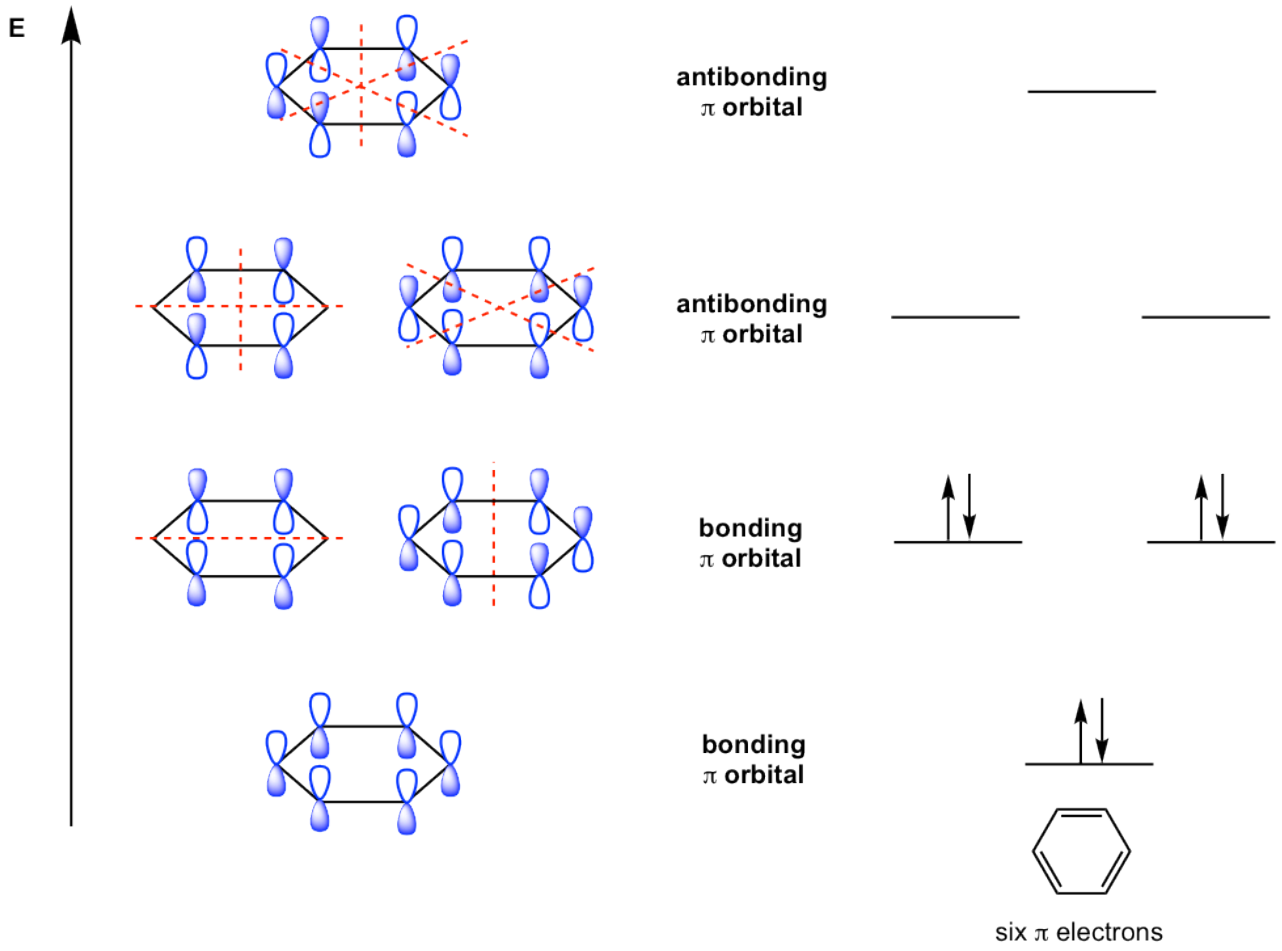


Fig. 4.2d π Molecular orbitals and π electron configurations of benzene

With six 2p orbitals combined, there are six π molecular orbitals, as shown in Fig. 4.2d. Three of them are bonding π MOs, and the other three are antibonding π MOs. Please note that one bonding π MO is in the lowest energy level, and the other two degenerate bonding π MOs are at the 2nd high energy level and both have one nodal plane. Similarly, there are two antibonding π MOs at the next energy level with two nodal planes for each one. The antibonding π MO at the highest energy level has three nodal planes. With a total of six π electrons for benzene, all the electrons occupy the bonding MOs, which accounts for the stability of benzene.

4.3 Hückel's Rule: Aromatic, Anti-aromatic and Non-aromatic Species

The term “aromatic” is used to describe the compounds that also have the ***special stability*** as benzene does. The special stability comes from the unique electronic structure features of aromatic compounds. To determine whether the structure of a compound meets the requirement to be “aromatic”, **Huckel’s rule** can be applied.

Huckel’s rule, which was proposed by German chemist and physicist Erich Hückel in 1931, states that a cyclic, planar molecule has 4n+2 π electrons and is aromatic. In other words, the molecule must meet the following criteria to be an ***aromatic* compound**:

- cyclic (a ring structure)
- planar (all atoms in the molecule lie in the same plane)
- fully conjugate (each atom has a p orbital)
- there are **4n+2** π electrons (n=0 or any positive integer)

Other than aromatic compounds that have special stabilities, a compound could also be classified as ***nonaromatic*** or ***antiaromatic***.

The cyclic compound that is not planar, or does not have all p orbitals fully conjugated, is **nonaromatic**. The nonaromatic compound is in the *same* energy level as the open-chain polyene with the same number of carbons.

The cyclic conjugated compound with **4n** π electrons is **antiaromatic.** The antiaromatic compound is in a *higher* energy level than open-chain polyene with the same number of carbons, which means the antiaromatic compound has unusual ***instability***.

Next, we will examine more cyclic structures by applying **Huckel’s** rule to determine which category a compound belongs to, aromatic, nonaromatic, or antiaromatic.

For the ring with 3, 5, or 7 carbons, there is always a sp^3 hybridized carbon that does not have the unhybridized p orbital, so the ring is not fully conjugated and is nonaromatic.

Cyclobutadiene, the ring with 4 carbons, has 4 π electrons, so is antiaromatic.

Cyclooctatetraene, the eight-membered ring, also has 8 π electrons. However it does not adopt the planar shape because of the stain, so it is nonaromatic.

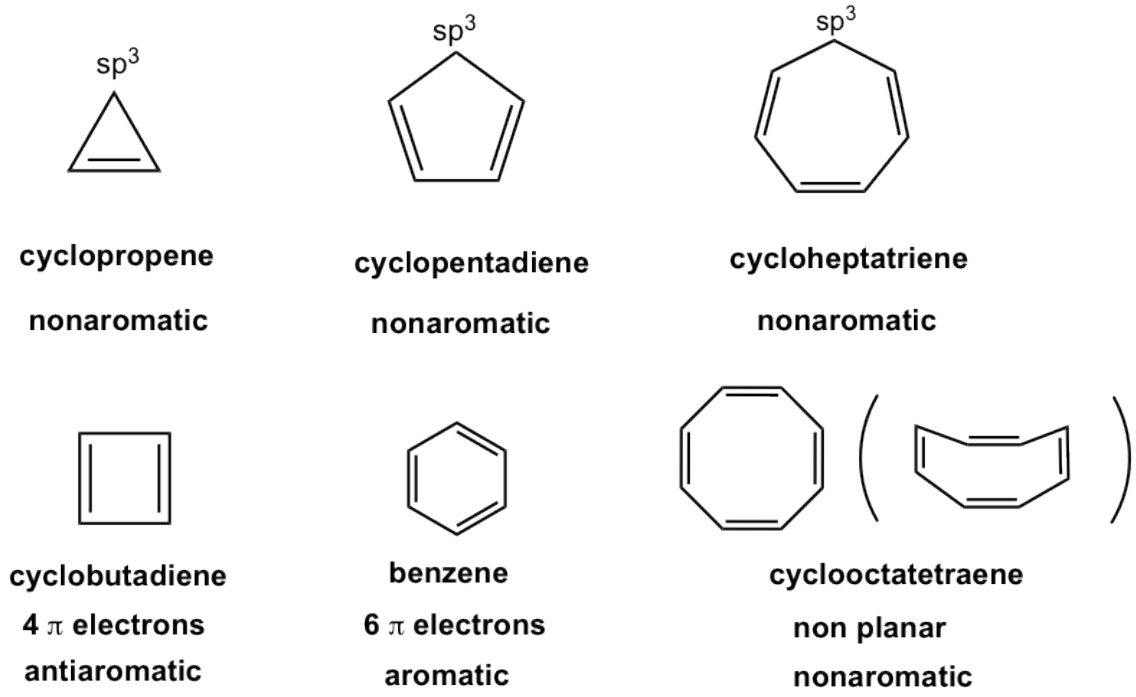


Fig. 4.3a Structures and Properties of cyclopolyenes from three to eight carbons

The properties of cyclopolyenes with three to eight carbons are summarized in Table. 4.1.

Annulene with an **odd** number of carbons			Annulene with an **even** number of carbons		
3-carbon ring	2 π **electrons** **non-conjugated**	**nonaromatic**	4-carbon ring	4 π **electrons**	**antiaromatic**
5-carbon ring	4 π **electrons** **non-conjugated**	**nonaromatic**	6-carbon ring	6 π **electrons**	**aromatic**
7-carbon ring	6 π **electrons** **non-conjugated**	**nonaromatic**	8-carbon ring	8 π **electrons** **non-planar**	**nonaromatic**

Table. 4.1 Summary of cyclopolyenes properties with three to eight carbons

With the size of the ring increasing, the term **annulene** can be incorporated. Annulene is the general name for

monocyclic compounds with a structure of alternating single and double bonds. The size of the ring is indicated by a number in the bracket. Benzene actually could be named [6] annulene, and cyclooctatetraene is [8]annulene.

For [10]annulene, there are two possible structures. However, planar shape is not favored for any of them because of the strains. [10]annulene is nonaromatic.

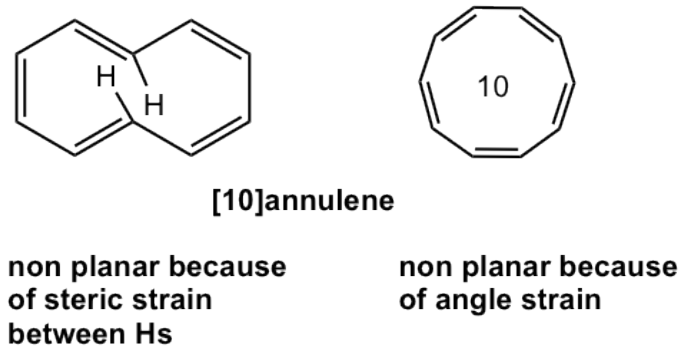


Fig. 4.3b Structures of [10]annulene

For annulenes with more carbons, the size of the ring is big enough to adopt a planar shape, without causing significant strains. So annulenes with 12 carbons or more are in planar shapes, and the property depends only on the total number of π electrons.

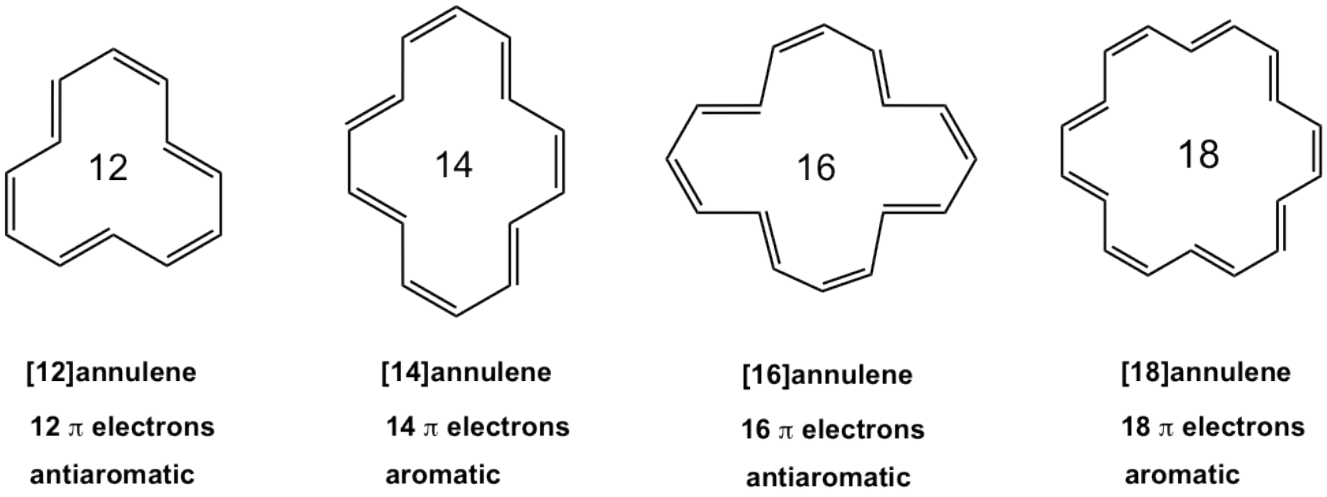


Fig. 4.3c Structures and properties of large-size annulenes

Polycyclic Aromatic Compounds

There are other types of aromatic compounds that contain more than one benzene rings. A representative type of

such compound is polycyclic aromatic compounds (also called benzenoid aromatic compounds) that have two or more benzene rings *fused* together. The term ***fused*** means that two aromatic rings are connected by at least one common carbon-carbon bond. Some examples of polycyclic aromatic compounds are shown in Fig. 4.3d.

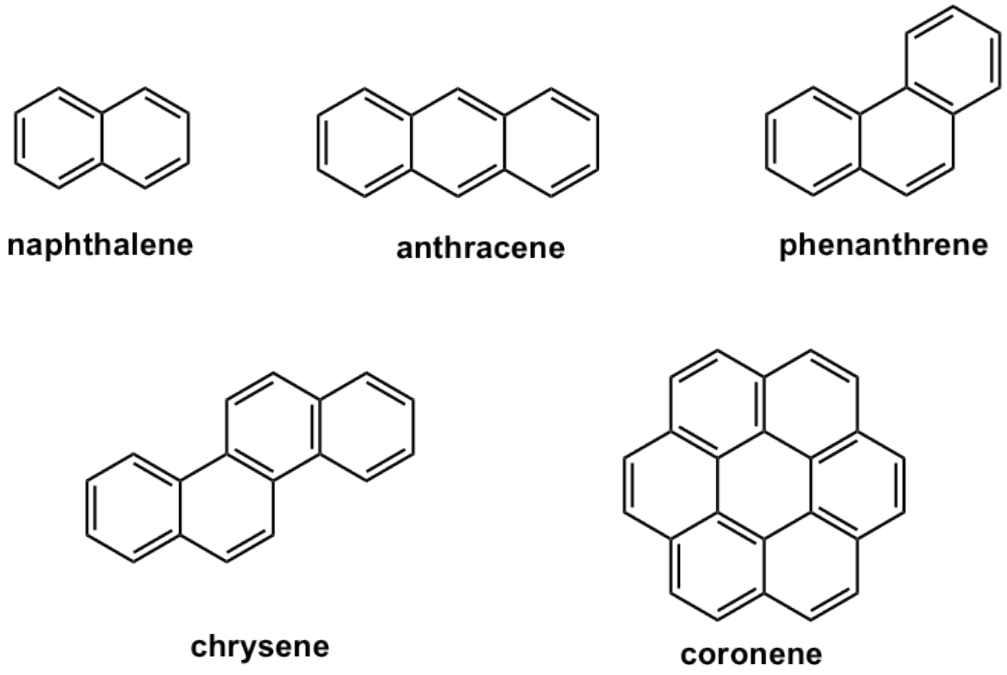


Fig. 4.3d Examples of polycyclic aromatic compounds

Naphthalene is a well-known polycyclic aromatic compound with two benzene rings fused together. As you may predict, the actual structure of naphthalene is a hybrid of three resonance structures, so it is highly stabilized by the resonance effect.

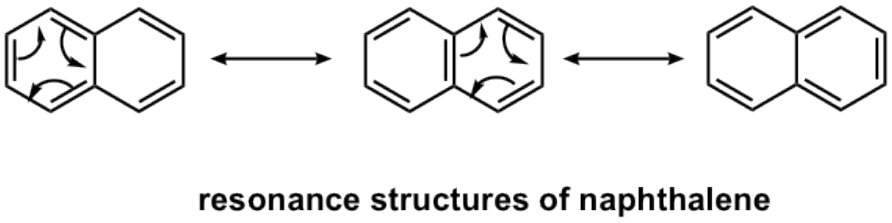


Fig. 4.3e Resonance structures of naphthalene

Aromaticity of Ions

Other than neutral molecules, some ionic species also show special stability due to aromaticity, and they are called aromatic ions. Huckel's rule applies to ions as well for determining the aromaticity.

A typical example is the cyclopentadienyl anion. The neutral cyclopentadiene molecule is nonaromatic as we learned earlier, however, this molecule is unusually acidic as a hydrocarbon and has a pK_a of about 16 (usually the pKa for

allylic hydrogen is about 40). The strong acidity of the molecule indicates that the conjugate base, cyclopentadienyl anion, should be exceptionally stable. The fact of the unusual stability of cyclopentadienyl anion can be explained by the aromaticity of the anion.

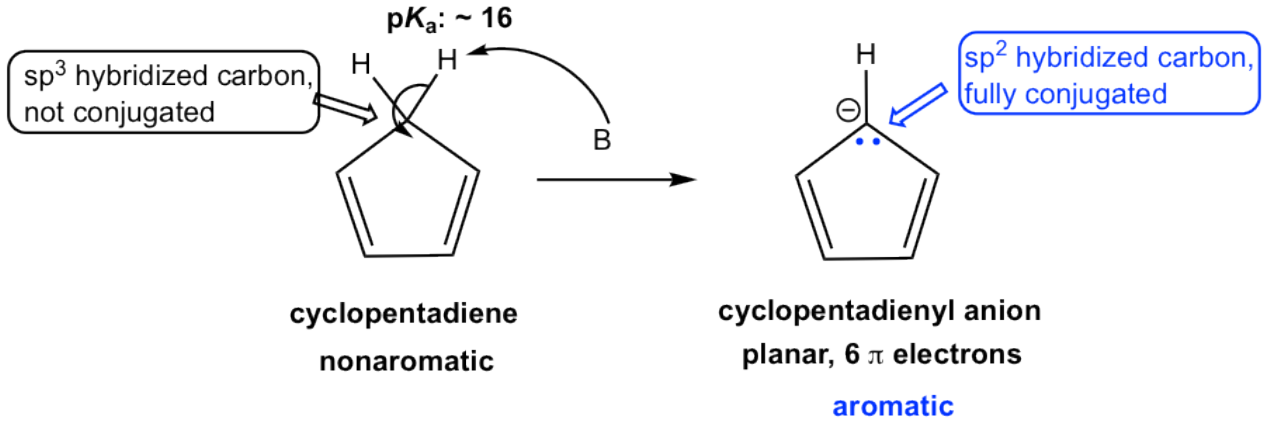


Fig. 4.3f High acidity of cyclopentadiene and aromaticity of cyclopentadienyl anion

After deprotonation, the initially sp^3 hybridized carbon gains one lone pair election and becomes a sp^2 hybridized carbon anion. The sp^2 carbon therefore has an unhybridized 2p orbital that can overlap with all the other four 2p orbitals to form a conjugated system. Moreover, with the lone pair electron occupying the 2p orbital, there are a total of 6 π electrons in the system, that is 2 (the lone pair) + 4 (two double bonds). A planar ring with conjugated π orbitals, and 6 π electrons, the cyclopentadienyl anion is an aromatic ion. The aromaticity of the anion explains the unusual acidity of the cyclopentadiene molecule.

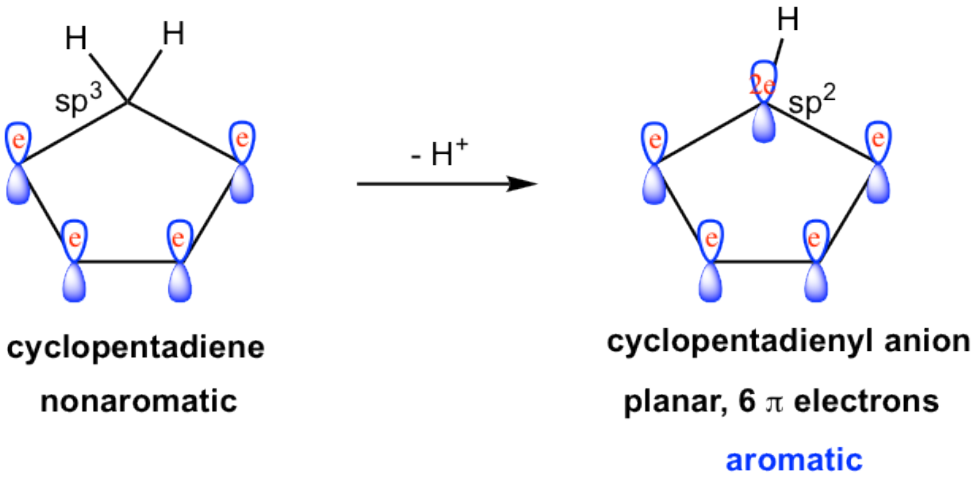


Fig. 4.3g π Orbitals of cyclopentadiene and cyclopentadieneyl anion

4.4 Heterocyclic Aromatic Compounds

A cyclic compound that includes elements other than carbon is called a heterocyclic compound. The most commonly involved heteroatoms are nitrogen, oxygen, and sulfur. Some heterocyclic compounds are also aromatic and show special stability. Examples of heterocyclic aromatic compounds are given here.

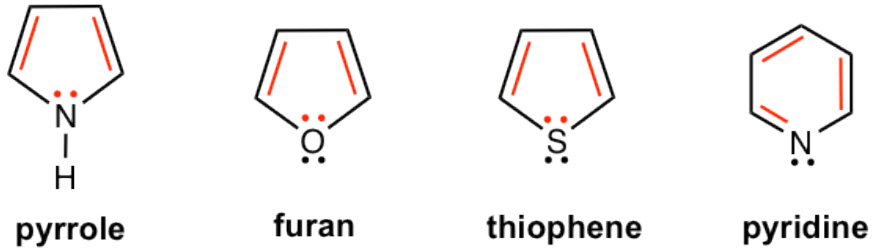


Fig. 4.4a Heterocyclic aromatic compound examples (electrons in the aromatic system are shown in red color)

Among the above examples, pyrrole, furan, and thiophene share similar structure features. All hetero elements, N, O, and S respectively, are in sp^2 hybridization. The unhybridized 2p orbital of N, O, and S holds one pair of lone-pair electrons, and the 2p orbital overlaps with the other four 2p orbitals of carbons (also in sp^2 hybridization) and forms the conjugated system. The total number of π electrons (shown in red color in Fig. 4.4a) for the conjugated system therefore is 6, that is 2+4, which matches Huckel's number and explains the aromaticity of the compounds.

The difference in the structure between pyrrole, furan, and thiophene is how the sp^2 hybrid orbitals are used for. For pyrrole, all three sp^2 hybrid orbitals are involved in bonding (N in pyrrole has three single bonds), while for furan and thiophene only two of the sp^2 hybrid orbitals used for sing bonds and the other sp^2 orbital carry one lone-pair electron (shown in black color in Fig. 4.4a). The black color electron pair is not part of the aromatic system. The structure differences between the three heterocyclic aromatic compounds are highlighted in Fig. 4.4b.

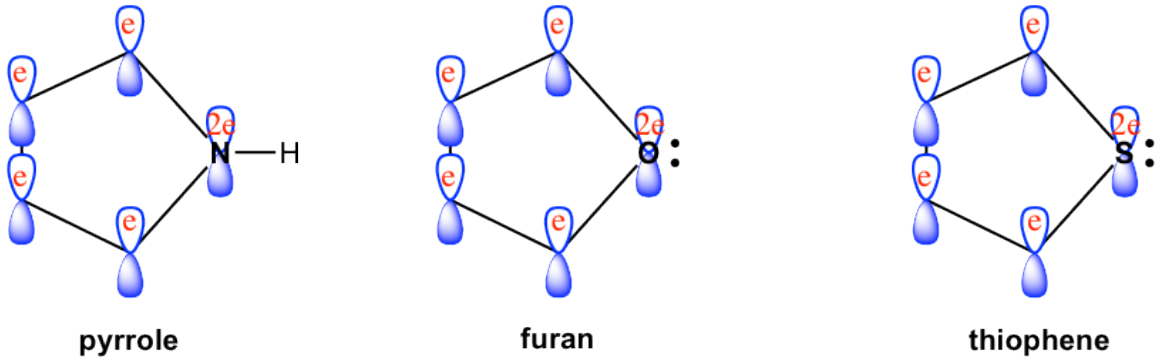


Fig. 4.4b Structure difference between pyrrole, furan, and thiophene

Pyridine is a six-membered ring that is similar to a benzene ring, but with a nitrogen atom. All the elements in pyridine are sp^2 hybridized, and the unhybridized 2p orbital for each element has one single electron that makes the total number of π electrons 6, the Huckel's number for aromatic (shown in red color in Fig. 4.4a). Another structural difference

between pyridine and benzene is that one of the sp^2 orbitals of nitrogen holds one lone pair electron, while all the sp^2 orbitals (for carbons) are used for bonding in benzene.

Pyrrole and Pyridine

Both pyrrole and pyridine are heterocyclic aromatic compounds with a nitrogen atom, and both nitrogen atoms have one pair of lone-pair electrons in the structure formula. Generally speaking, the nitrogen with lone pair electron should show basicity. It turns out that, however, **pyridine is basic but pyrrole is not.** How do you explain the difference in basicity between the two compounds?

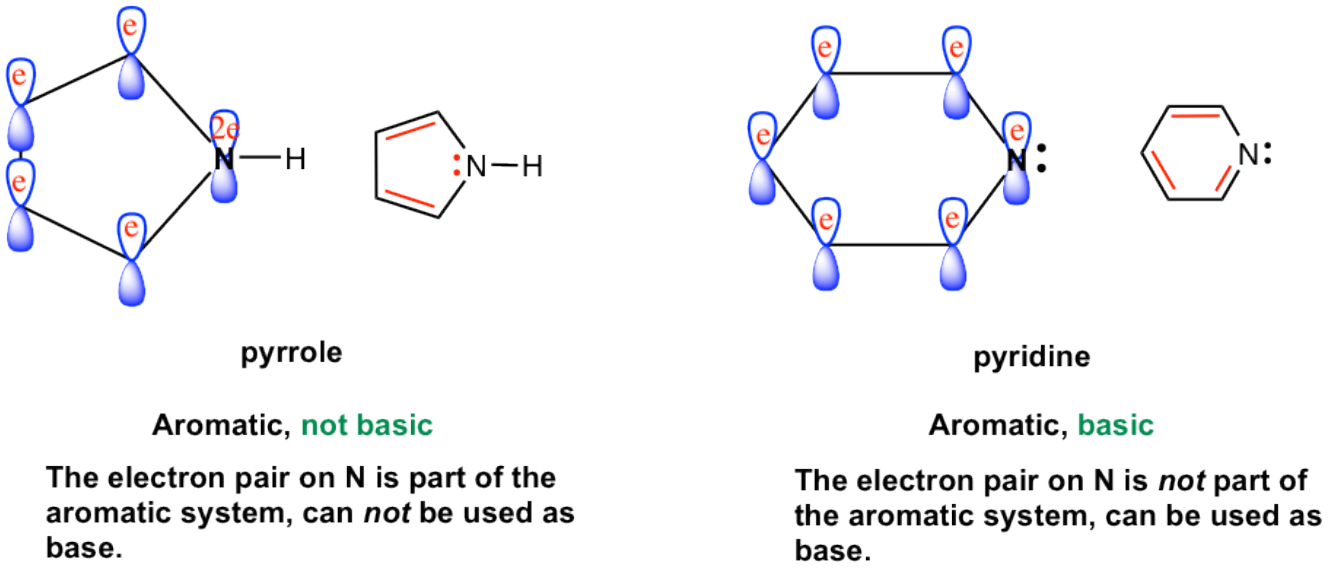
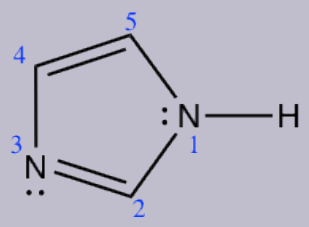


Fig. 4.4c Structure and basicity difference between pyrrole and pyridine

Such differences can be interpreted by taking a closer look at the structure of each (Fig. 4.4c). In pyridine, the lone pair electron (black color) is in the sp^2 orbital of nitrogen and is ***not*** part of the aromatic system, therefore it can be used as a base. In pyrrole, the lone pair electron on nitrogen (red color) is in the unhybridized 2p orbital and **is** part of the aromatic system. Being part of the aromatic system prevents the electron pair from being used as a base, or not available for reacting with a proton. Thus pyrrole is not appreciably basic.

Example

Imidazole has two nitrogens, only one is basic. Predict and explain which nitrogen atom is basic.



imidazole

Answer:

The nitrogen atom in the #3 position is more basic, with the same reason for the basicity of pyrrole that the lone pair electron of that N is not part of the π system.

4.5 Electrophilic Aromatic Substitution (EAS) of Aromatic Compounds

Reactivities of aromatic compounds arise from their electronic properties, that is the aromaticity (or special stability) of these compounds. To retain the special stability, benzene does not undergo addition reactions like other alkene. Instead, substitution is the most common reaction for benzene and other aromatic compounds.

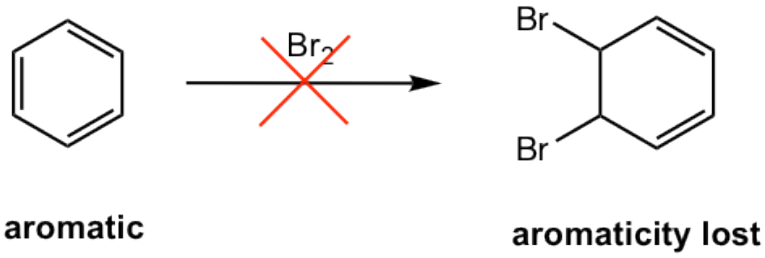


Fig. 4.5a Benzene does not undergo addition

In a substitution reaction, one or more hydrogens on benzene can be replaced by a variety of different groups, for example, halogen, alkyl group, or carbonyl group, this provides the chance to produce huge numbers of different derivates of benzene. Since the benzene ring is very electron-rich (with six π electrons), it attracts electrophile and **electrophilic aromatic substitution (EAS)** is the most common substitution mechanism for benzene.

Electrophilic Aromatic Substitution (EAS)

Electrophilic aromatic substitution of benzene is the reaction in which an electrophile replaces one of the hydrogen atoms of the benzene ring.

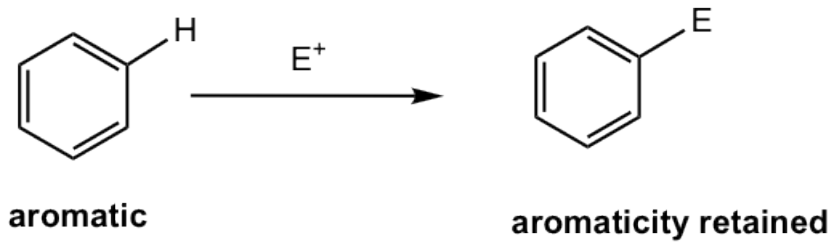


Fig. 4.5b General EAS reaction equation

Depending on the group introduced onto the benzene ring, the reaction can also be named in a specific way, such as halogenation, nitration, etc. The five most common and useful EAS reactions are summarized in Fig. 4.5c. These

reactions provide synthetic routes to a variety of benzene derivatives that have great applications in the synthesis of many other important compounds.

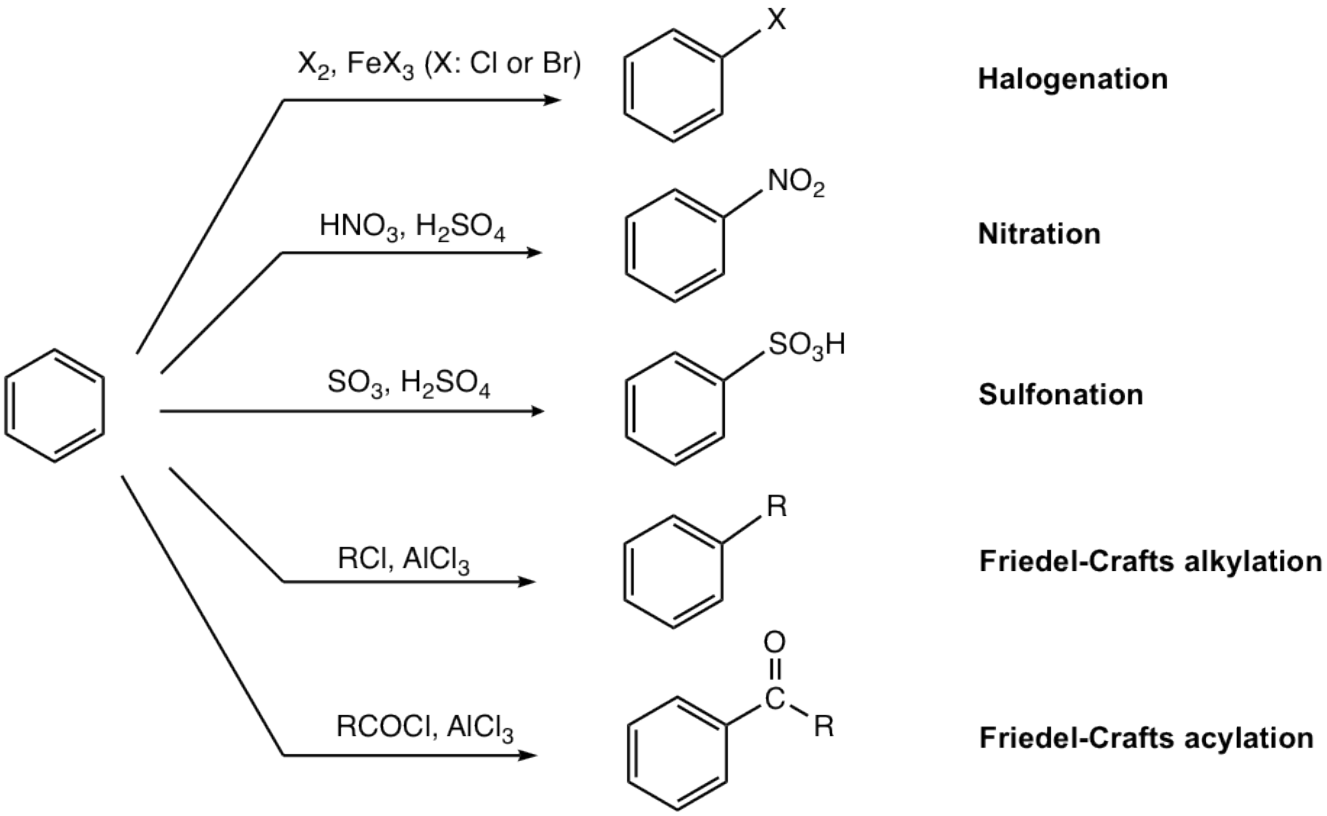


Fig. 4.5c Common EAS reactions of Benzene

General Mechanism for EAS

The functional groups involved in different EAS reactions seem rather different, however, they all follow the same general mechanism. The difference only lies in the different structures of the electrophile for each type of EAS reaction. "E" is used to represent electrophiles in the general mechanism below (Fig. 4.5d).

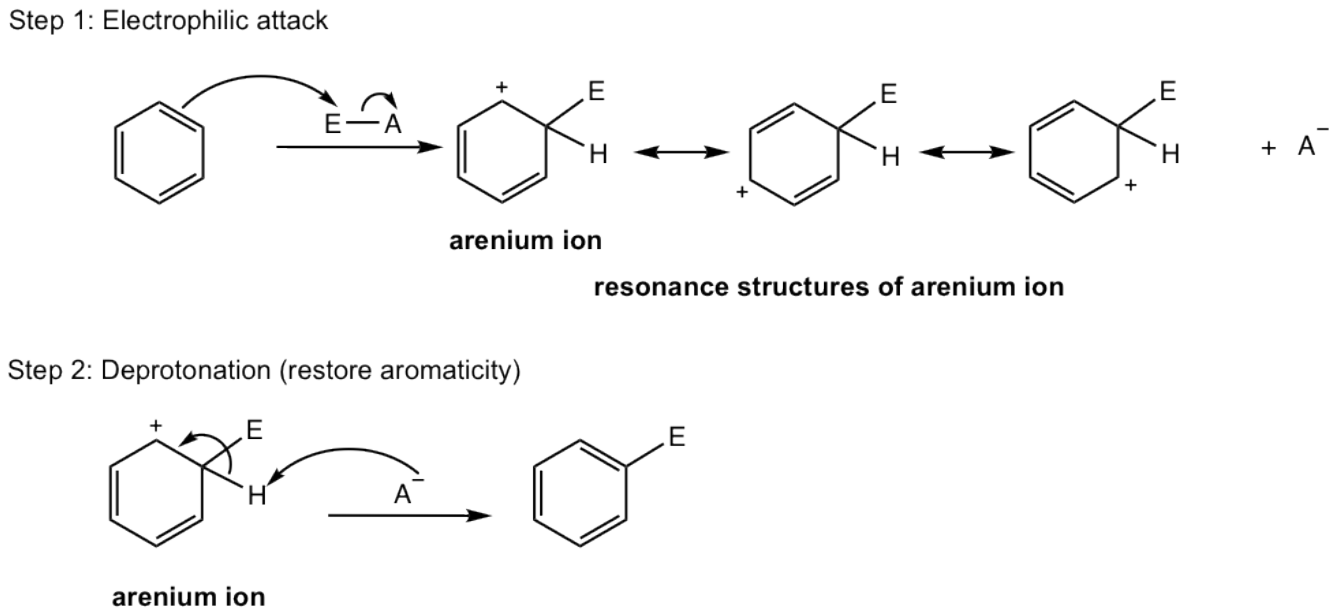


Fig. 4.5d General mechanism for EAS reaction of benzene

In the first step of the EAS, one electron pair of the benzene π system reacts with the electrophile, and this electron pair transfer forms a new σ bond. As a result, the electrophile is connected to one of the carbon atoms of the benzene ring, and a nonaromatic carbocation intermediate is formed which is called the **arenium ion**.

Formation of this arenium ion interrupts the aromatic system. **Arenium ion**, which is a cyclohexadienyl carbocation, has four sp^2 hybridized carbons with a total of four π electrons, and it is nonaromatic. The carbocation intermediate is still stabilized by the resonance effect though, as shown in the mechanism.

In the 2^{nd} step, a proton is removed from the carbon atom that bonds with the electrophile, and the aromaticity is restored in the substitution product.

In the following sections, we will examine the details of each type of EAS reaction. As mentioned earlier all the reactions follow the same general mechanism, the major differences are the ***structures*** of different electrophiles and***the generation of the electrophiles***.

4.6 Common EAS Reactions

4.6.1 Halogenation

Halogenation of benzene requires halogen (Cl_2 or Br_2) together with Iron (III) halide as a catalyst, for example, $FeCl_3$ with Cl_2, or $FeBr_3$ with Br_2 specifically. $AlCl_3$ can be used for chlorination as well.

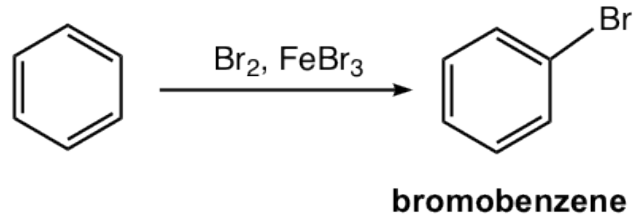


Fig. 4.6a Bromination of benzene

Iron (III) halide acts as Lewis acid in the mechanism, to make the halogen a stronger electrophile and facilitates the reaction. No halogenation reaction takes place for benzene without Lewis acid. The detailed mechanism is shown in Fig. 4.6b with bromination as an example.

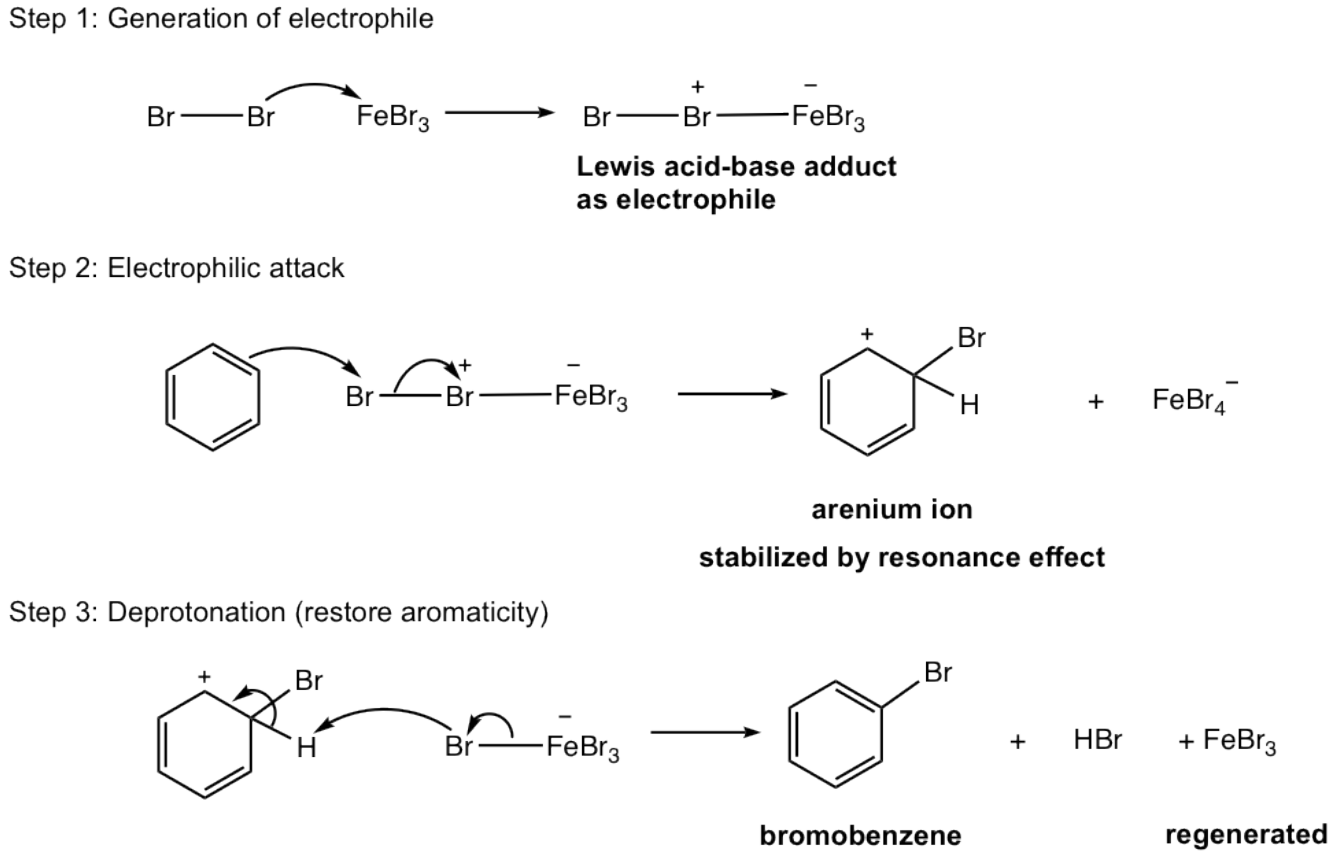


Fig. 4.6b Mechanism for halogenation (bromination) on benzene

The bromine molecule is non-polar, so the bromine atom is not electrophilic enough to react with benzene directly. In the presence of Lewis acid $FeBr_3$, the Lewis acid-base adduct is formed between $FeBr_3$ and Br_2. The Br-Br bond is polarized in the adduct and one bromine bears a positive charge, so it can react with benzene as a stronger electrophile.

While the generation of halogen electrophile is unique for halogenation, the following two steps are standard as shown in the general mechanism (Fig. 4.5d). Iron (III) bromide, the catalyst, is regenerated in the last step and can be reused in the reaction.

4.6.2 Nitration

Nitration reaction on benzene takes place with a mixture of concentrated nitric acid and concentrated sulfuric acid. Special attention is required to handle the concentrated acids mixture, which is a very strong corrosive oxidizing reagent.

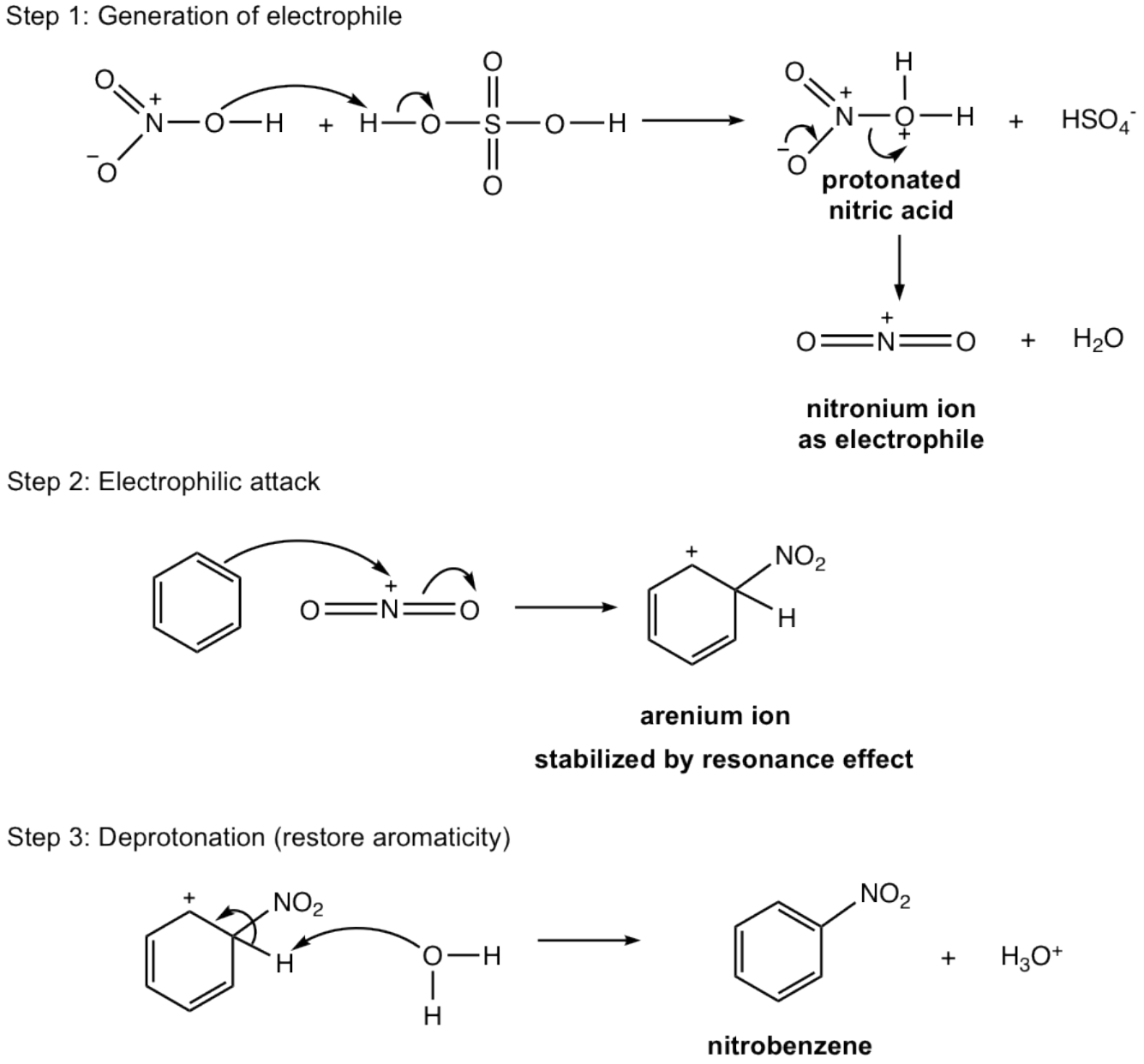


Fig. 4.6c Mechanism for halogenation (bromination) on benzene

Again the most important and unique step for nitration mechanism is the generation of electrophile, NO_2^+, nitronium ion. In the first step, nitric acid is protonated by sulfuric acid (the stronger acid), and the protonated nitric acid dissociates to produce nitronium ion and water. Nitronium ion is the electrophile for nitration reaction to complete the following two standard steps, and produce nitrobenzene product.

4.6.3 Sulfonation

Benzene undergoes sulfonation when reacts with fuming sulfuric acid. Fuming sulfuric acid is sulfuric acid with sulfur trioxide (SO_3) gas dissolved. When sulfur trioxide is protonated by sulfuric acid, the SO_3H^+ cation is produced and acts as an electrophile for the sulfonation reaction, in which the benzenesulfonic acid is produced as a final product.

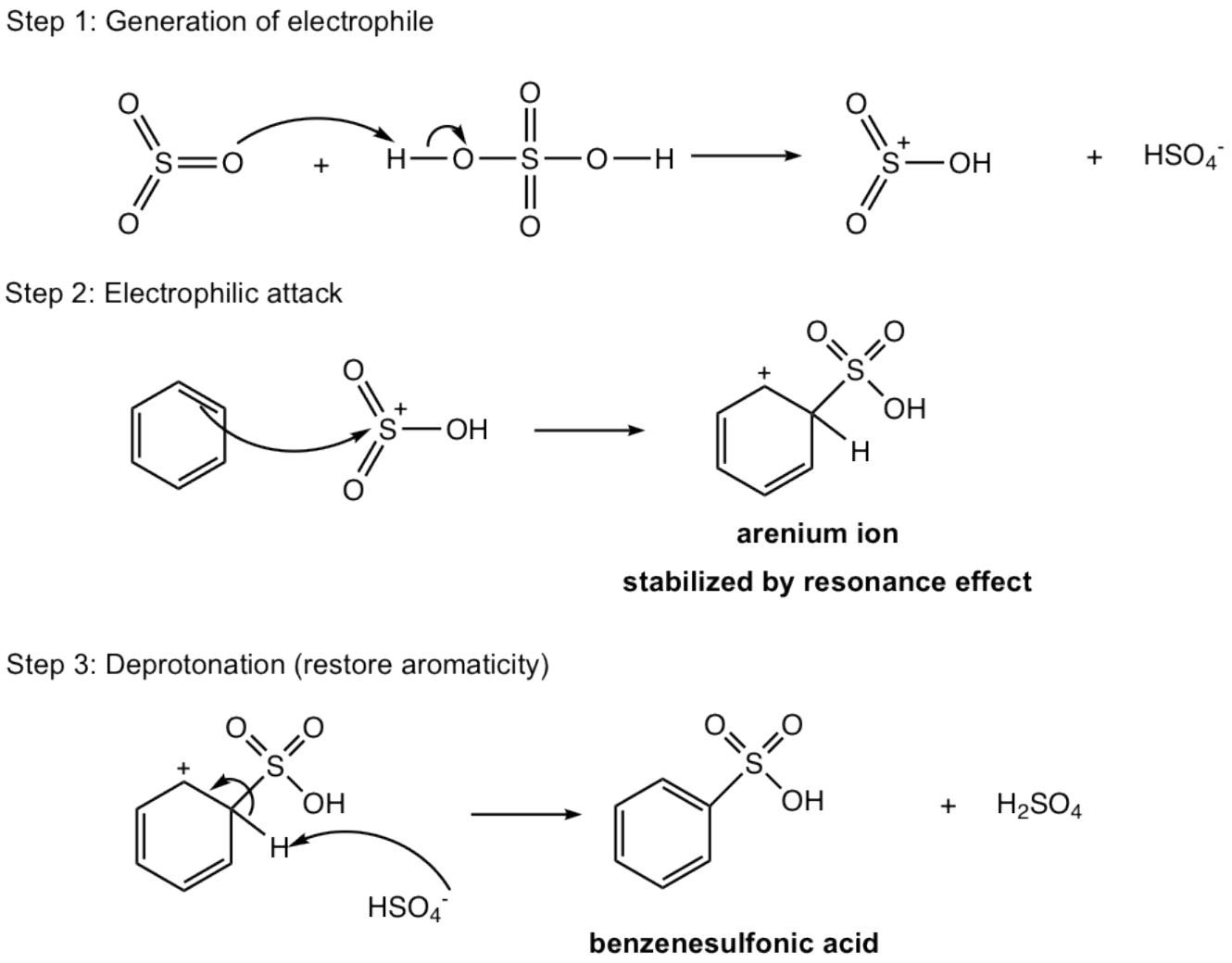


Fig. 4.6d Mechanism for sulfonation on benzene

A special feature of this reaction is that the process is reversible, which means the benzenesulfonic acid can also be converted back to benzene. The position of the equilibrium depends on the reaction condition applied. Fuming sulfuric acid should be used to produce the sulfonation product, while the diluted sulfuric acid with heat allows the removal of the sulfonic acid group, or desulfonation, as illustrated in Fig. 4.6e.

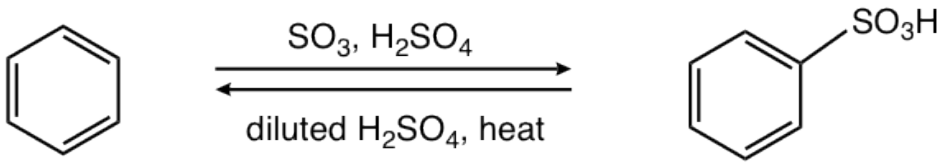


Fig. 4.6e Reversibility of sulfonation on benzene

The reversibility of the sulfonation reaction makes the sulfonate group a suitable choice of the "blocking" group for the synthesis of benzene derivatives. The Sulfonate group is first introduced on the benzene ring to "block" a certain position, further substitutions occur next with other groups introduced onto other positions of the benzene ring, and the sulfonate group is removed at the end when no longer needed. Application of this strategy will be discussed in **section 5.3**.

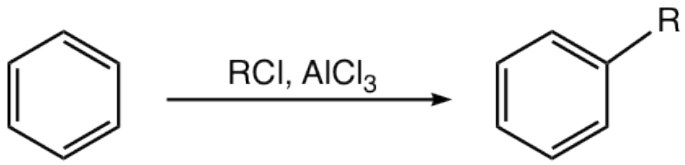
4.7 Friedel–Crafts Reactions

Friedel–Crafts reactions are also EAS. In the EAS reactions we learned so far, groups with heteroatoms (halogen, nitrogen, and sulfur) are introduced onto the benzene ring. Friedel–Crafts reactions are the methods to introduce carbon-containing groups onto the ring, as a result, they are of special interest in organic synthesis to build up larger molecules from smaller units like the benzene. They are so important that are discussed here in a separate section.

Friedel-Crafts reactions were discovered by Charles Friedel, a French scientist, and his collaborator American scientist James Crafts, in 1877. They are the methods for the preparations of alkylbenzenes (alkyl group, R) and acylbenzenes (acyl group, COR, or COAr), and are called Friedel–Crafts alkylation and Friedel–Crafts acylation respectively.

4.7.1 Friedel–Crafts Alkylation

The general equation for an alkylation reaction is shown here.



Friedel-Crafts alkylation

Fig. 4.7a General equation of Friedel-Crafts alkylation

Aluminum chloride, $AlCl_3$, also acts as the Lewis acid catalyst here (similar to the case of halogenation), to form a complex with an alkyl halide and generate carbocation that acts as an electrophile to react with the benzene ring. This is illustrated in the first step of the mechanism (Fig. 4.7b), the generation of electrophile.

Mechanism for Friedel–Crafts Alkylation

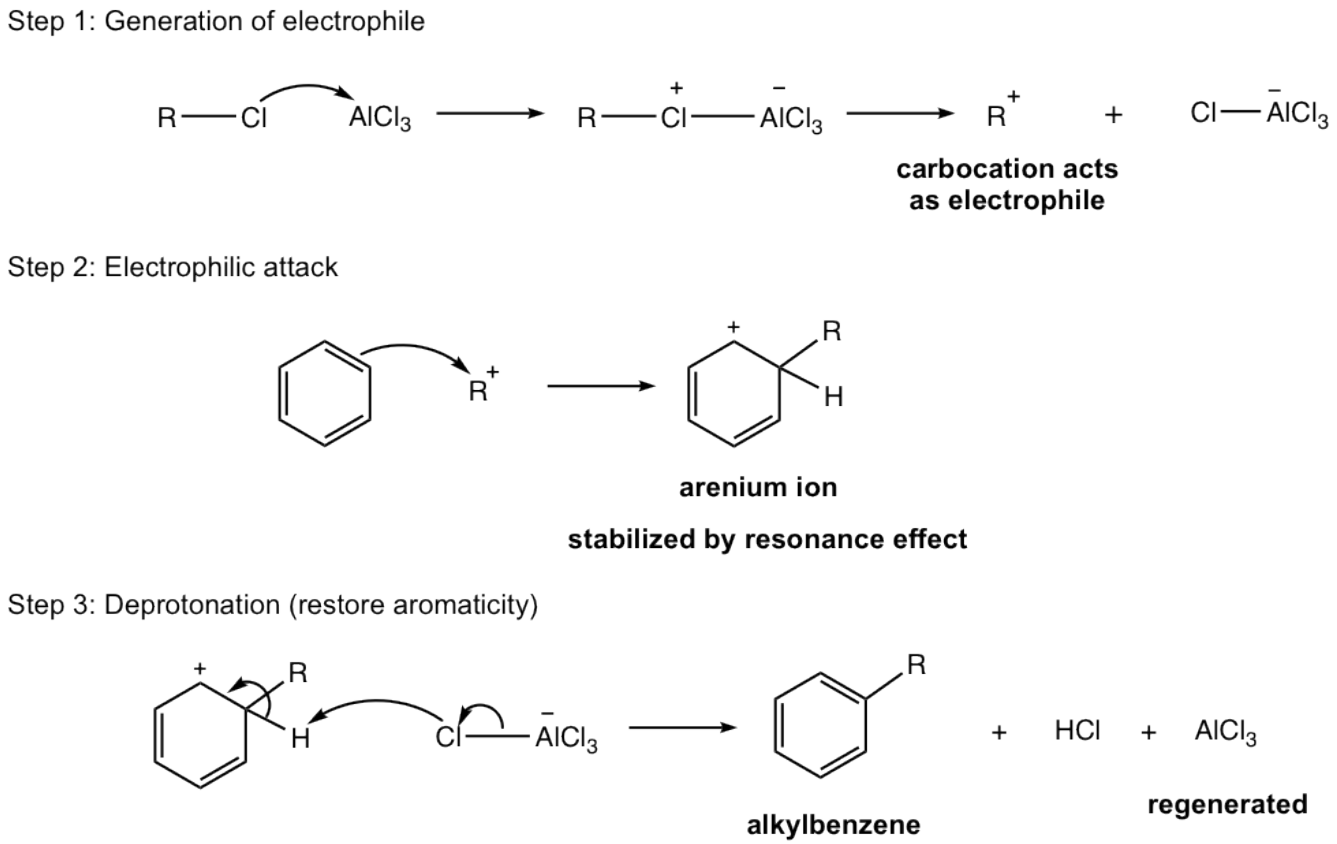
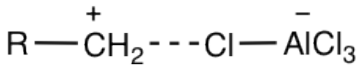


Fig. 4.7b Mechanism of Friedel–Crafts Alkylation

A couple of extra notes for the alkylation reaction:

- Other Lewis acids could also be used as catalysts, for example, BF_3, $SbCl_5$, and $AlBr_3$.
- The reaction works well for primary, secondary, and tertiary halides. Since the primary carbocation does not form however because of the low stability, the complex of $AlCl_3$ with RCH_2Cl acts as the electrophile.



alkyl halide and Lewis acid complex

Fig. 4.7c Alkyl halide and Lewis acid complex

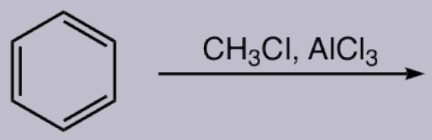
- Even though such a complex (in Fig. 4.7c) is not a real carbocation, it works so much like a carbocation and also undergoes carbocation **rearrangement** when available (reaction #3 in the following example). This brings a problem or limitation for the alkylation.
- Carbocation can be generated by other methods as well, for example by a mixture of alkene and an acid, or by dehydration of alcohol in the presence of acid, as shown in reactions #4 and #5 of the examples below.

- Another problem with alkylation is that **polyalkylation** might occur. Once an alkyl group is introduced into the benzene ring, it activates the ring towards further EAS because the alkyl group is electron-donating (further discussion on activating effect in **Section 5.1**).

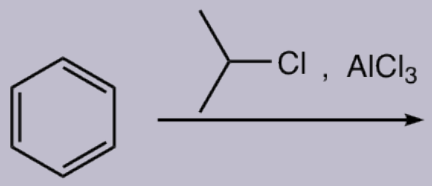
Examples

Show the alkylation product.

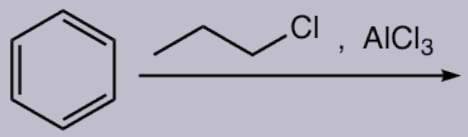
1)



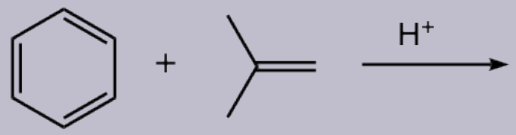
2)



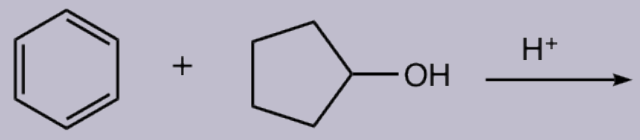
3)



4)

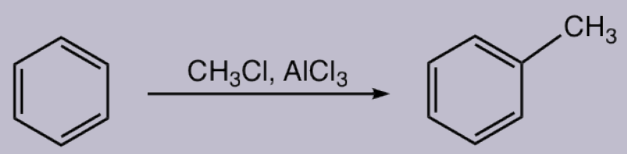


5)

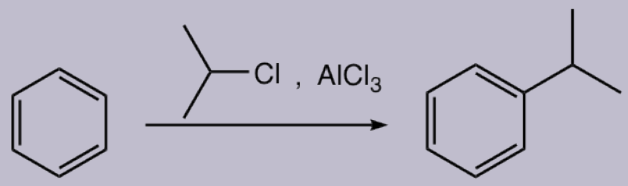


Answers:

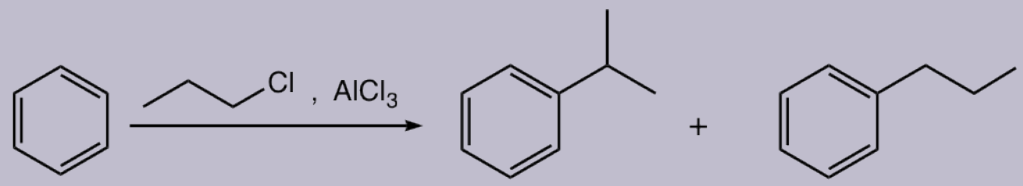
1)



2)



3)

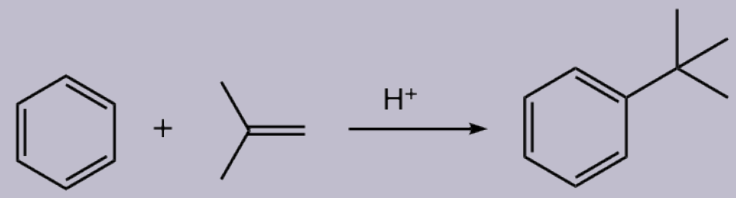


major

minor

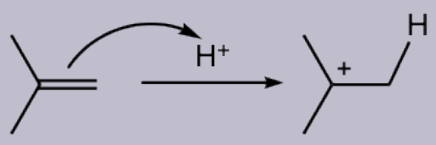
more stable 2° carbocation by rearrangement

4)

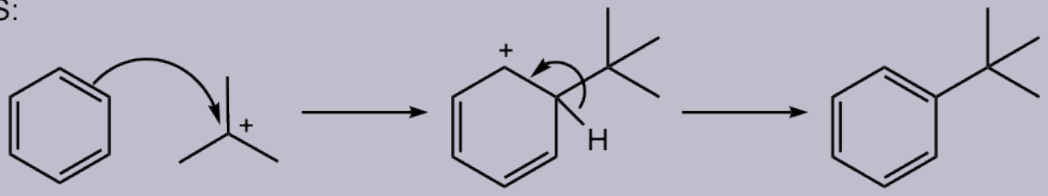


In this reaction, the carbocation intermediate is generated by the protonation of alkene, and then reacts with the benzene ring by EAS.

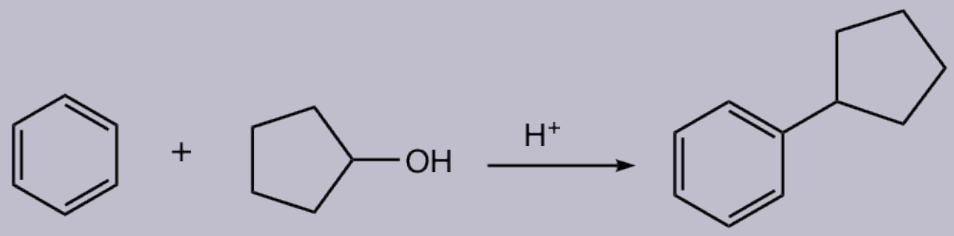
Generation of carbocation:



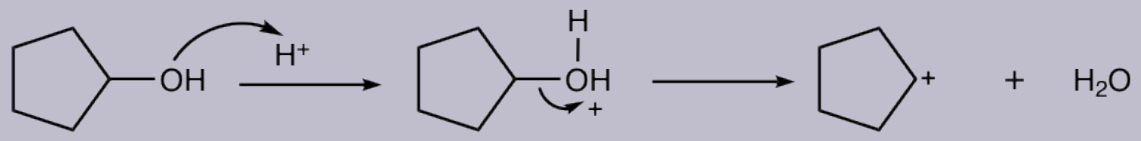
EAS:



5)

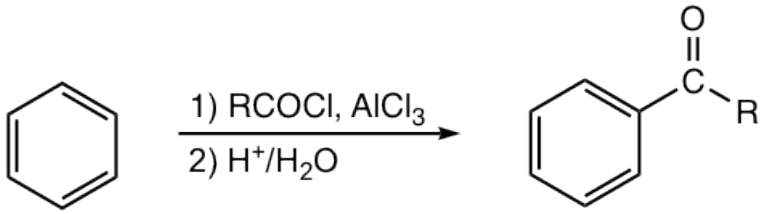


For this reaction, the carbocation intermediate is generated by dehydration of alcohol in the presence of acid, then reacts with the benzene ring by EAS.



4.7.2 Friedel–Crafts Acylation

The acyl group (COR, or COAr) is introduced into the benzene ring in the acylation reaction. The reagent usually employed for this purpose is the mixture of Lewis acid and acyl halide, as shown in Fig. 4.7d. The detailed mechanism will be discussed next in Fig. 4.7e.



Friedel-Crafts acylation

Fig. 4.7d General equation of Friedel–Crafts acylation

Mechanism for Friedel–Crafts Acylation

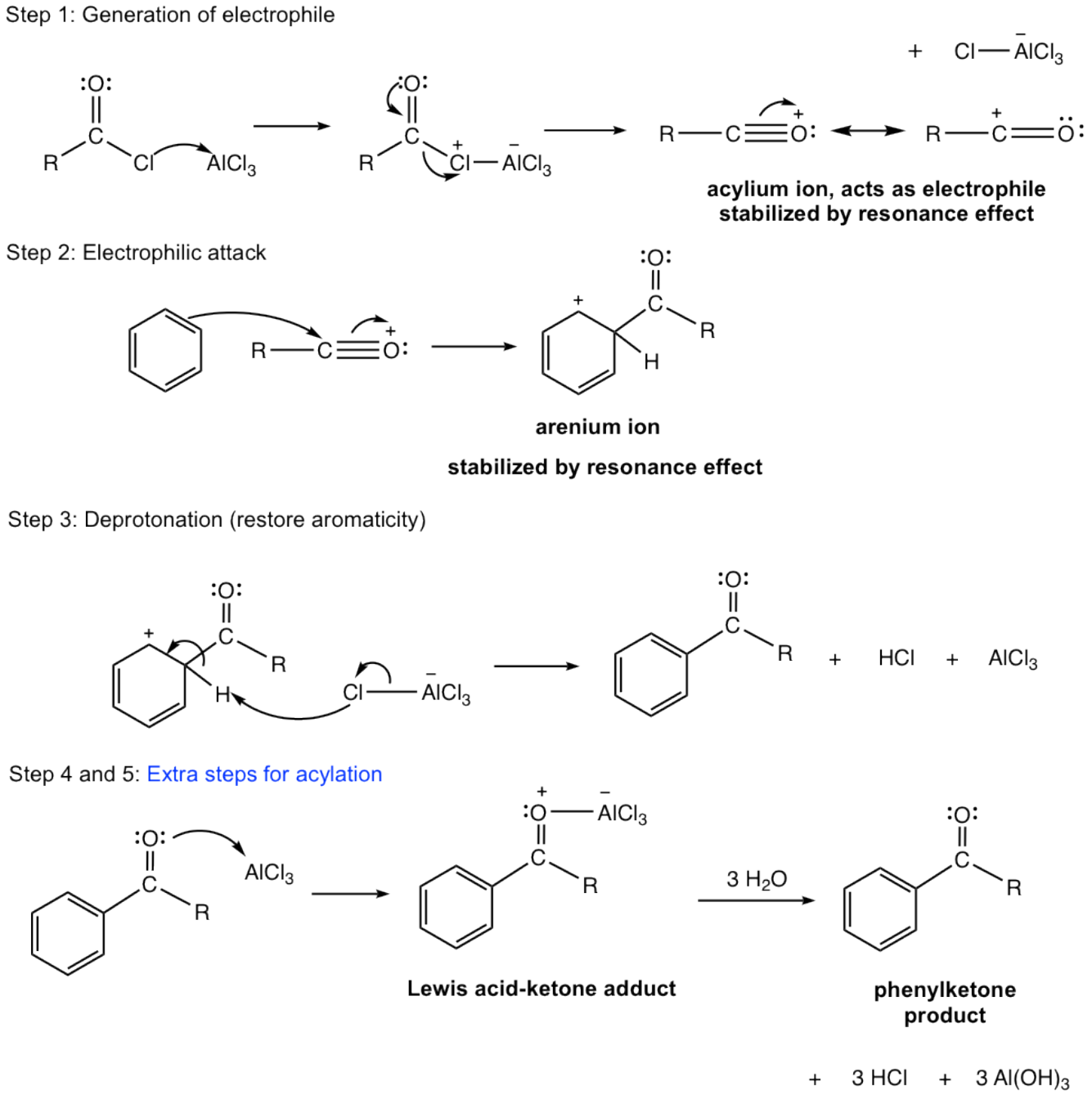


Fig. 4.7e Mechanism for Friedel–Crafts acylation

With the aid of Lewis acid, the halogen atom in acyl halide leaves and the acylium ion is generated in the first step. Acylium ion acts as an electrophile to react with the benzene ring. The following steps, steps 2 and 3, electrophilic attack and deprotonation, are standard in the EAS mechanism.

A special part of acylation is that two extra steps (steps 4 and 5) take place. After step 3, Lewis acid is still present in the reaction mixture, and it forms an adduct with ketone that acts as a Lewis base because of the lone pair electron on

the oxygen atom. To get ketone as a final product, the work-up step with acidic water, therefore, is necessary to liberate the ketone from the adduct. For this reason, the **two-step** reaction consequences (shown in the general equation and examples next) are required for the acylation overall reaction condition.

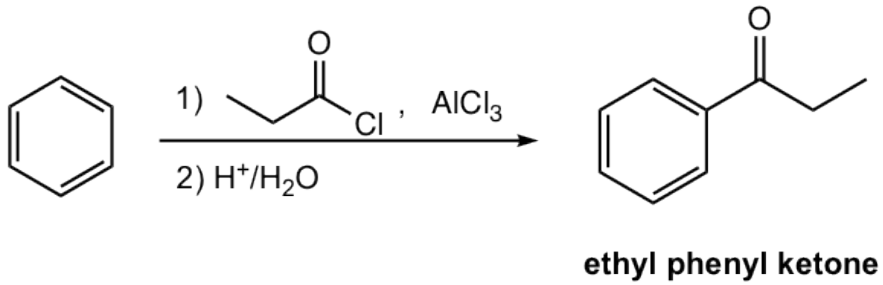


Fig. 4.7f Synthesis of ethyl phenyl ketone by Friedel–Crafts acylation

Please note a few other points for reagents used in the Friedel–Crafts acylation.

- Acyl chloride can be prepared by reacting carboxylic acid with thionyl chloride with heat.

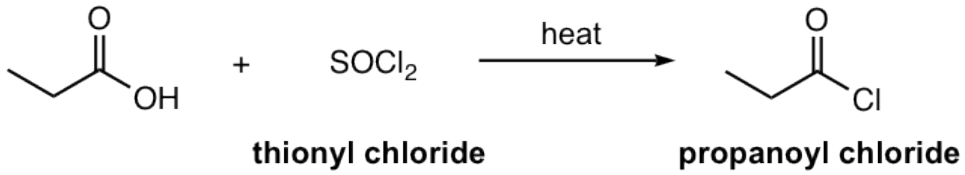


Fig. 4.7g Preparation of acyl halide

- Other than acyl halide, carboxylic acid anhydride can also be used for Friedel–Crafts acylation. Lewis acid is still required for anhydride, and the reaction mechanism is almost the same. The side product of using anhydride is the corresponding carboxylic acid.

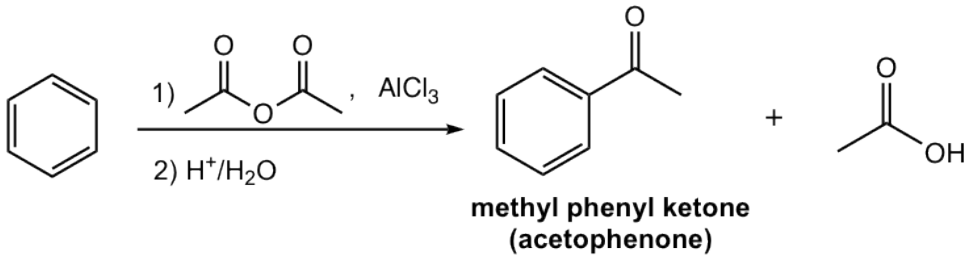


Fig. 4.7h Application of anhydride in Friedel–Crafts acylation

4.7.3 Application of Friedel-Crafts Acylation in Synthesis

Friedel-Crafts alkylation provides a way to introduce an alkyl group into the benzene ring directly, however, it has problems with **rearrangement** and **polyalkylation** as mentioned in **section 4.7.1**. So it is not an ideal method to synthesize mono-substituted benzene with an unbranched alkyl group.

Such problems don't apply to acylation though. No rearrangement occurs for the acylium ion, the electrophile for acylation, since it is stabilized by the resonance effect. Furthermore, because of the deactivation of the product (refer to **Section 5.1**), the acylated benzene ring is no longer susceptible to further EAS, so no polyacylation. Therefore, if the acyl group is first introduced on the benzene ring, then reduced to the alkyl group, i.e., **acylation + reduction** could be a better alternate to synthesize unbranched alkylbenzene. This strategy has been proven successful and applied broadly in synthesis. The general equation is shown in Fig. 4.7i.

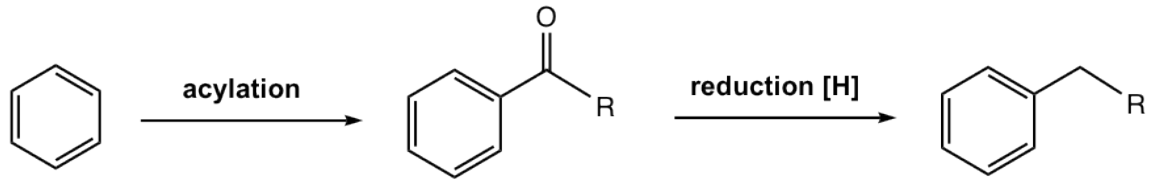


Fig. 4.7i Acylation followed by reduction as an alternative route to alkylation

Reduction of Ketone to Methylene

Two methods are commonly applied to reduce the acyl group (ketone) to a methylene group.

Clemmensen Reduction

The reducing agent used in Clemmensen reduction is the metal amalgam of zinc and mercury, with strong acid (concentrated HCl) and heat.

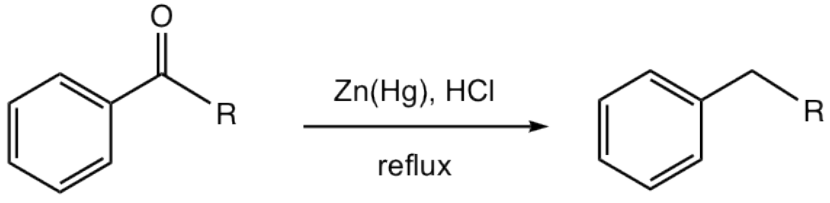


Fig. 4.7j Clemmensen Reduction

Wolff-Kishner Reduction

As we have learned in **section 2.7.2,** the hydrazone derivative of ketone can be further reduced to alkane when reacted in a strong base condition with KOH at a very high temperature.

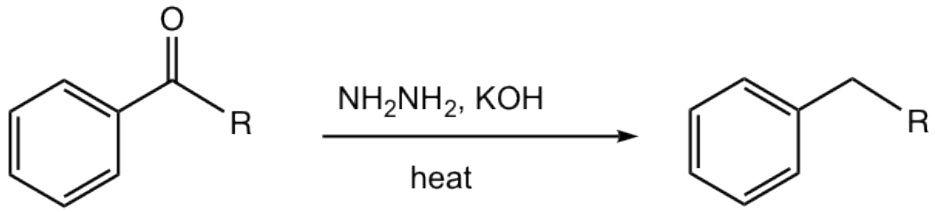
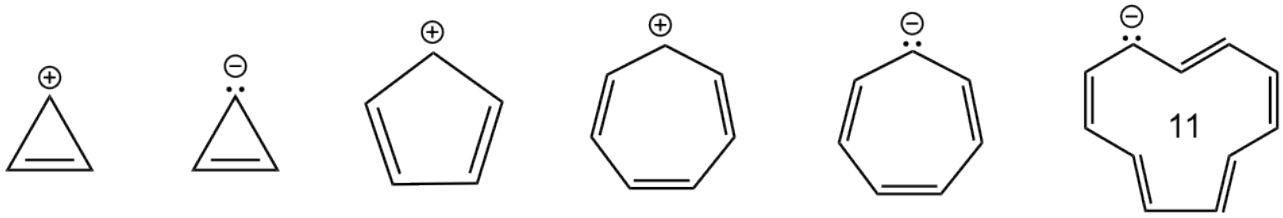


Fig. 4.7k Wolff-Kishner Reduction

These two methods are complementary to each other, with Wolff-Kishner reduction involving base, and acid needed in Clemmensen reduction.

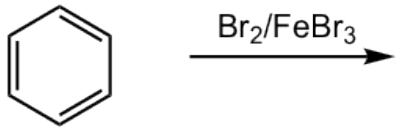
4.8 Practices

1. Indicate each of the following ions would be aromatic, antiaromatic, or nonaromatic.

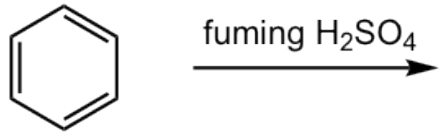


2. Show the product of the following reactions.

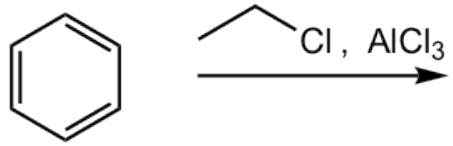
a.



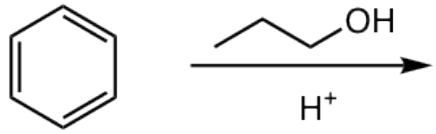
b.



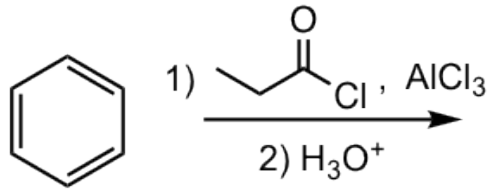
c.



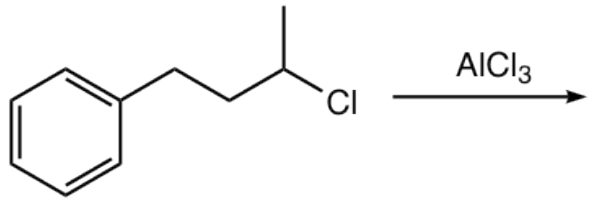
d.



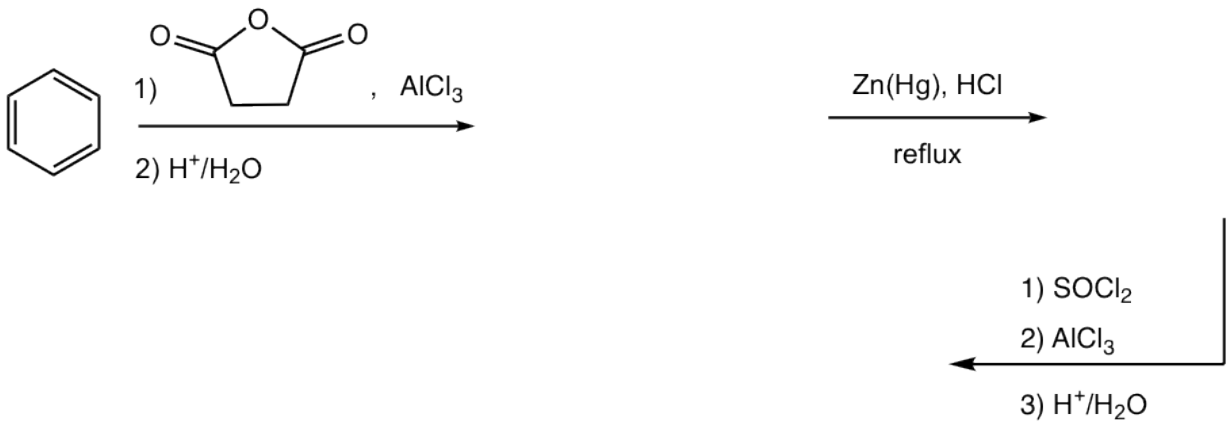
e.



f.



g.


1)
, $AlCl_3$
2) H^+/H_2O
Zn(Hg), HCl
reflux
1) $SOCl_2$
2) $AlCl_3$
3) H^+/H_2O

4.9 Practices Answers

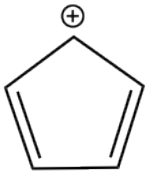
1. Indicate each of the following ions would be aromatic, antiaromatic, or nonaromatic.

2 π electrons

aromatic

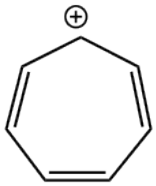
4 π electrons

antiaromatic



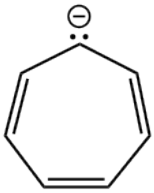
4 π electrons

antiaromatic



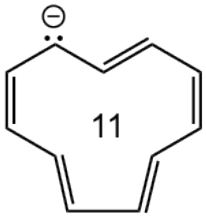
6 π electrons

aromatic



8 π electrons

antiaromatic

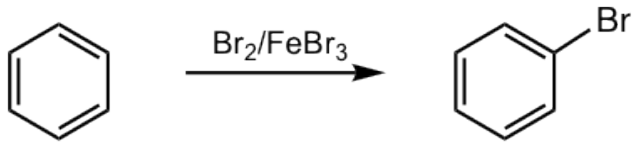


12 π electrons

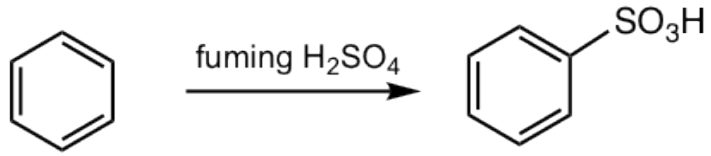
antiaromatic

2. Show the product of the following reactions.

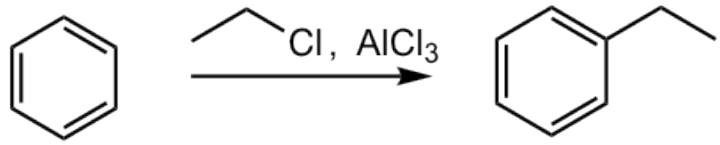
a.



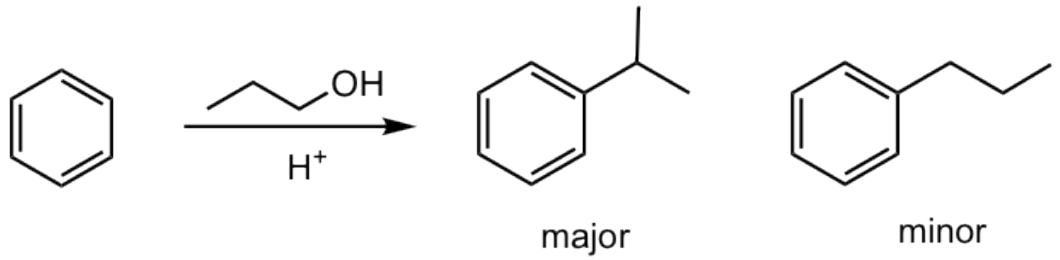
b.



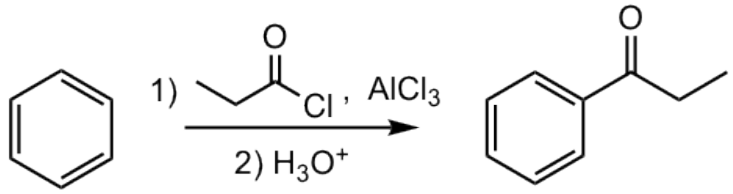
c.



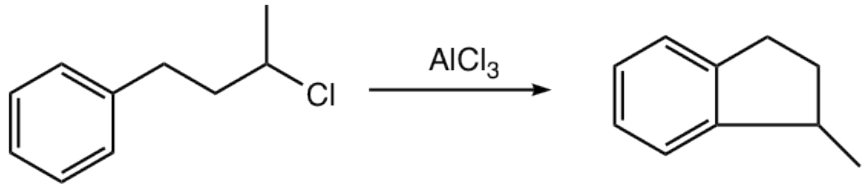
d.


OH
H+
major
minor

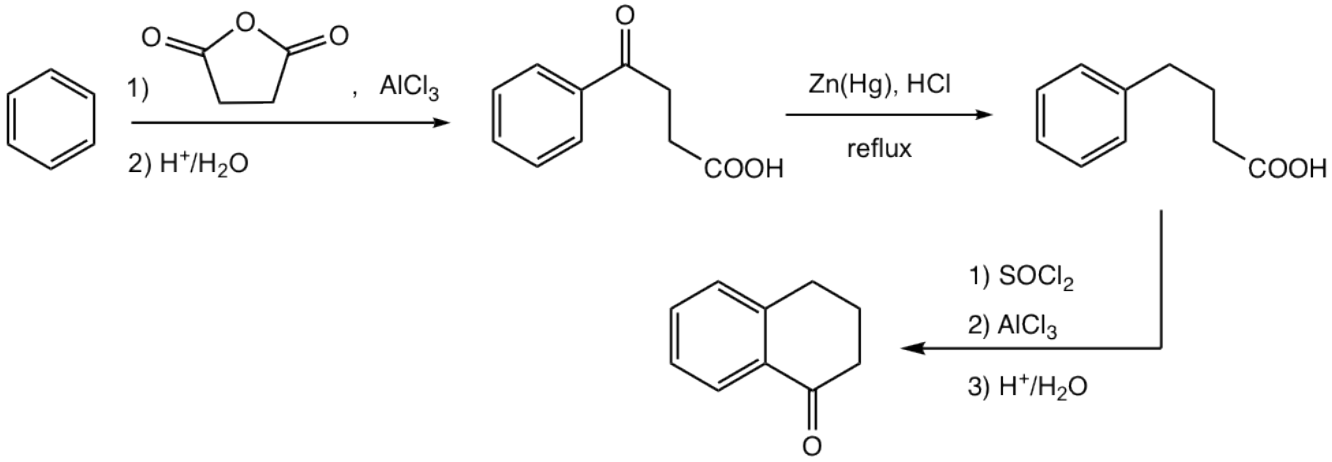
e.


O
1)
Cl
AlCl3
2) H3O+
O

f.


Cl
AlCl3

g.


O
O
O
1)
2) H+/H2O
AlCl3
O
COOH
Zn(Hg), HCl
reflux
COOH
1) SOCl2
2) AlCl3
3) H+/H2O
O

CHAPTER 5: MORE REACTIONS ON AROMATIC COMPOUNDS

5.1 Activating or Deactivating Effect of the Substituents on EAS

We have had thorough discussions about EAS reactions on the benzene rings in **Chapter 4**. EAS reaction also takes place on substituted benzenes, and the substituent already present on the benzene ring has important effects on further EAS reaction.

When substituted benzene undergoes EAS reactions, the substitute that is on the benzene ring has effects on two aspects, that will be discussed here and in **section 5.2**.

- Activating or deactivating effect: change the reactivity of the ring toward EAS;
- Directing effect: affects the orientation of the incoming group on the ring.

The **activating group** is the substituent that makes the ring **more reactive** than benzene towards EAS, i.e., reacts faster.

- Electron-donating groups make the benzene ring more electron-rich, and more reactive towards the electrophile, so **electron-donating groups are activating groups**.

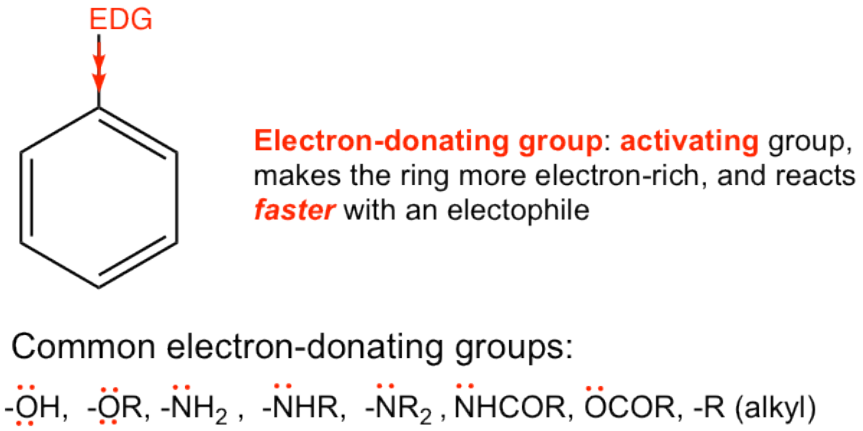

EDG
Electron-donating group: activating group, makes the ring more electron-rich, and reacts faster with an electophile
Common electron-donating groups:
-OH, -OR, -NH2 , -NHR, -NR2 , NHCOR, OCOR, -R (alkyl)

Fig. 5.1a Common electron-donating (activating) groups

The **deactivating group** is the substituent that makes the ring **less reactive** than benzene towards EAS, i.e., reacts more slowly.

- Electron-withdrawing groups make the benzene ring electron-poor, and less reactive towards the electrophile, so **electron-withdrawing groups are deactivating groups**.

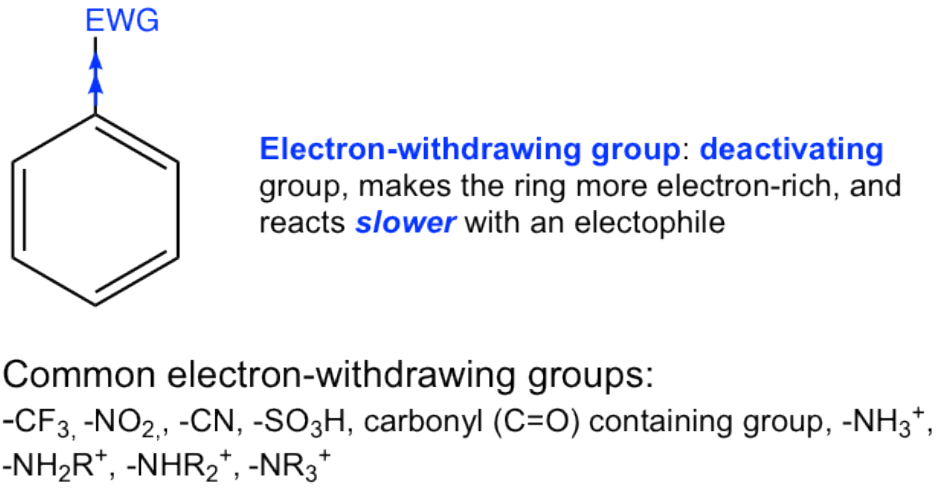

EWG
Electron-withdrawing group: deactivating
group, makes the ring more electron-rich, and
reacts slower with an electophile
Common electron-withdrawing groups:
-CF3, -NO2, -CN, -SO3H, carbonyl (C=O) containing group, -NH3+,
-NH2R+, -NHR2+, -NR3+

Fig. 5.1b Common electron-withdrawing (deactivating) groups

How to Identify a Group Is Electron-Donating or Electron-Withdrawing Group?

A quick ***hint*** to tell if a group is electron-donating or electron-withdrawing is to check whether the atom that connects directly to the benzene ring has lone-pair electrons.

The group that has lone-pair electrons on the atom attached directly to the benzene ring is an electron-donating group.

The group that does not have lone-pair electrons on the atom attached directly to the benzene ring is an electron-withdrawing group.

The above trends don't apply to alkyl group (electron-donating) and halogens (electron-withdrawing).

The above trend provides a quick hint for us to "memorize" the properties of groups, however, understanding the actual reasonings behind them is more important.

Understanding the Electronic Property of a Group

Alkyl groups

Alkyl groups are electron-donating because of the hyperconjugation effect, the effect we have learned in **section 7.4 in Book I**. The orbitals of the sigma bonds in the alkyl group overlap partially with the p orbital of the sp^2 carbon in the benzene ring, so the electron density of the ring increases. The hyperconjugation effect is a rather weak effect to donate electrons, so alkyl groups are weak electron-donating groups.

Groups with heteroatom that contain lone-pair electrons

For groups with heteroatoms, most commonly N and O, there are two effects that work the opposite way. The inductive effect of the electronegative atom makes the group electron-withdrawing, while the resonance effect from the lone-pair electrons of the atom makes the group electron-donating. For most groups, the contribution through the resonance effect is stronger than the inductive effect, so most such groups (except halogens) are electron-donating. This is demonstrated in Fib. 5.1c with the OH group as an example.

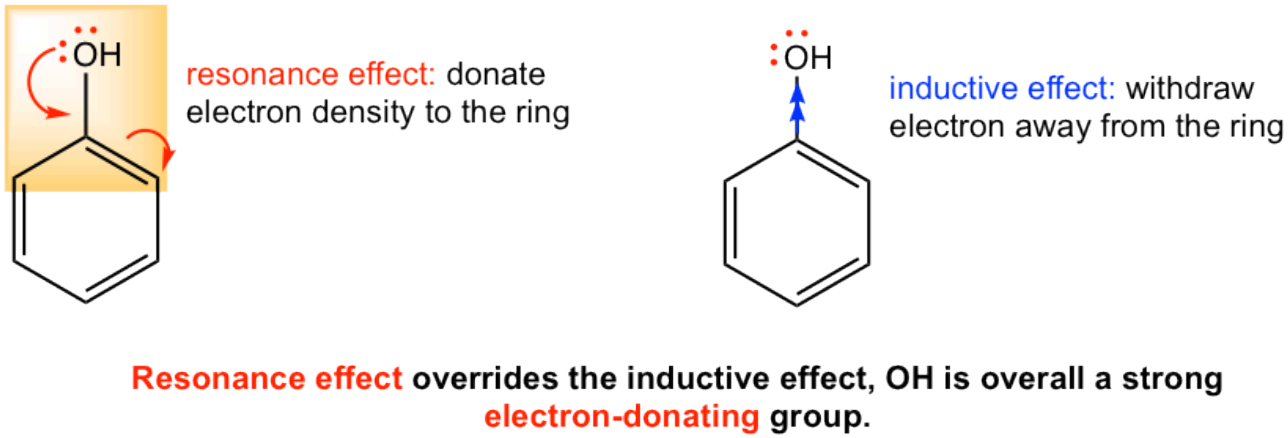

OH
resonance effect: donate electron density to the ring
OH
inductive effect: withdraw electron away from the ring
Resonance effect overrides the inductive effect, OH is overall a strong electron-donating group.

Fig. 5.1c OH group is electron-donating

Halogens

Detailed discussions on halogens will be given in **section 5.2**.

Groups with multiple bonds

For substituents with multiple bonds, for example, -CN, $-NO_2$, SO_3H, and -C=O, resonance structures are available because of the multiple bonds. Such resonance effect works in the way of pulling electron density away from the

benzene ring, therefore the groups with multiple bonds are electron-withdrawing. The example of the carbonyl group is shown in Fig. 5.1d.

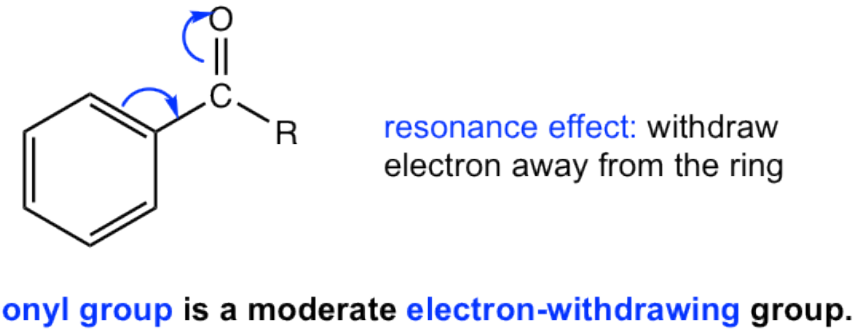


Fig. 5.1d Carbonyl group is electron-withdrawing

Groups with Heteroatom that does not contain lone-pair electrons

Inductive effect (because of the high electronegativity of the heteroatom, and positive charge for some groups) is the only effect involved for such groups since there are no lone-pair electrons available. Such groups are strongly electron-withdrawing groups, as the example of NH_3^+ in Fig. 5.1e.

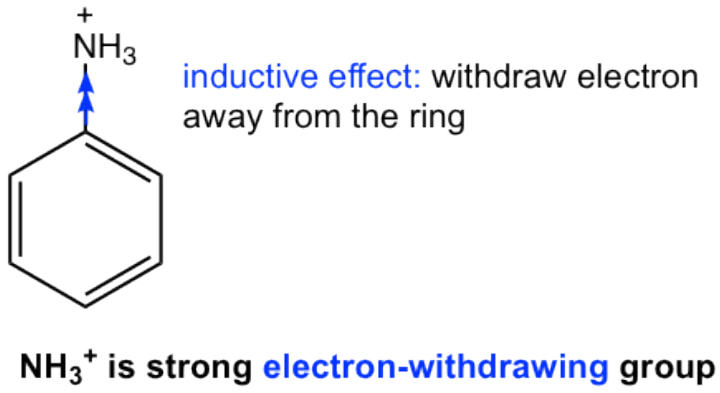


Fig. 5.1e NH_3+ group is electron-withdrawing

5.2 Directing Effects of the Substituents on EAS

A substituent on the benzene ring also influences the orientation that the incoming EAS takes place (i.e., which position the incoming group occupies), this is the directing effect. There are two types of directors specifically: ortho-para directors and meta directors.

5.2.1 Two Types of Directors: Ortho-para Directors or Meta Directors

If the substituent on the benzene ring is an ortho-para director, the incoming group will be directed (oriented) to the ortho- and para-position of the director itself.

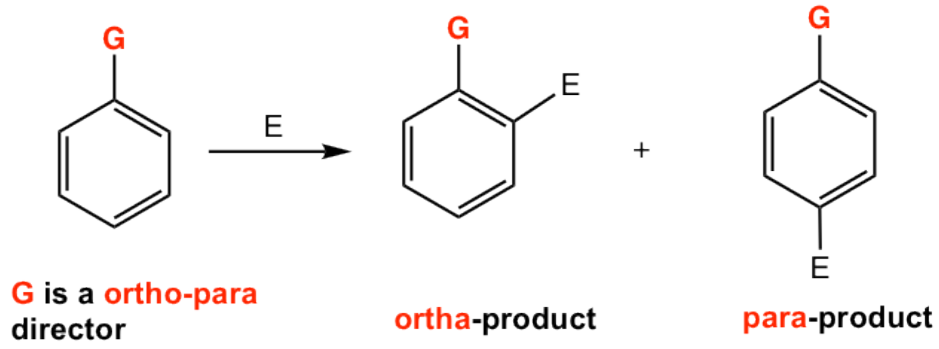


Fig. 5.2a The effect of ortho-para director

If the substituent on the benzene ring is a meta director, the incoming group will be directed (oriented) to the meta-position of the director itself.

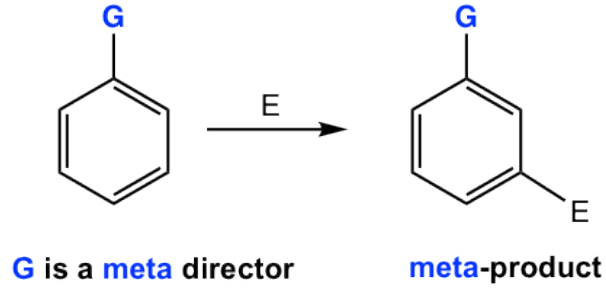


Fig. 5.2b The effect of meta director

The directing effect of a substituent is closely related to the activating-deactivating effect, specifically:

- **Activating groups are ortho-para directors;**
- **Deactivating groups (except halogens) are meta directors;**
- **Halogen substituents are weakly deactivating groups, and are ortho-para directors.**

In this section, we will take a closer look at the directing effects of different groups, from the experimental results, to compare and get the trending. The explanations for why the directing effect works in a certain way will be discussed in the next section **5.2.3.**

Let's start with some experimental results.

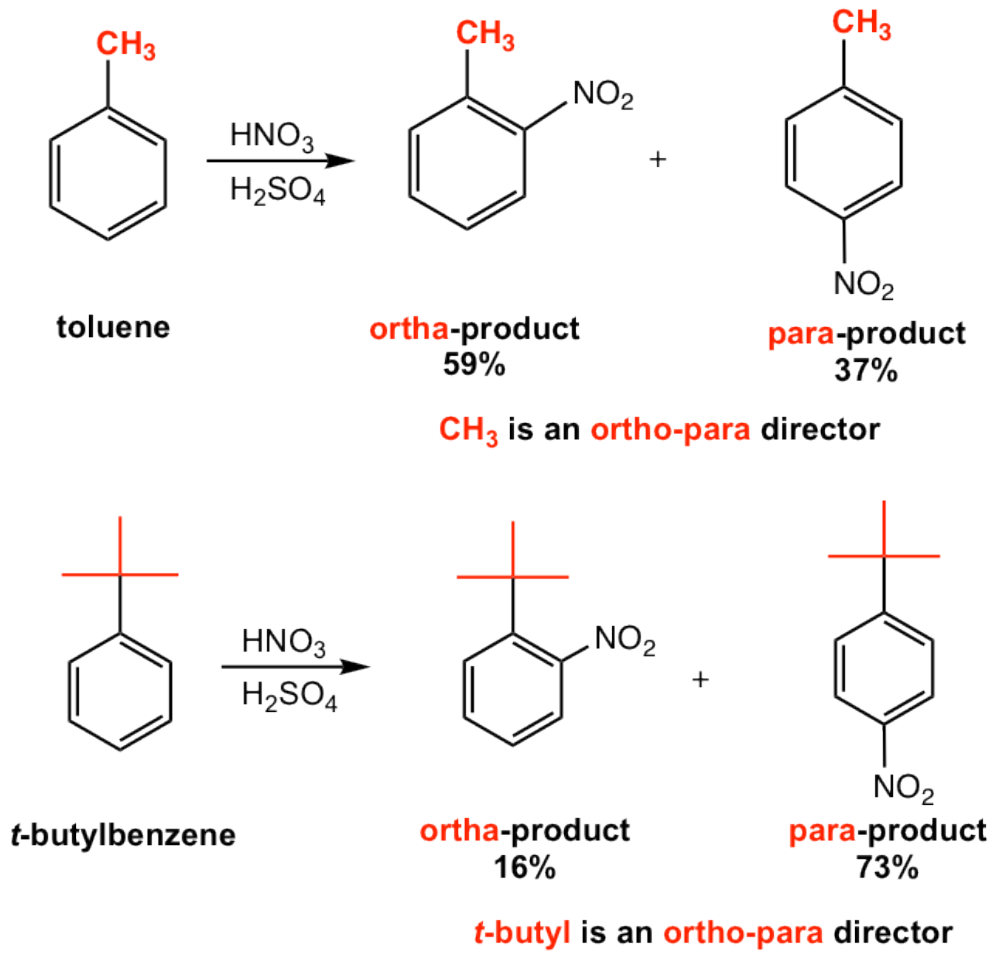


Fig. 5.2c Nitration reaction of toluene and t-butylbenzene

The experimental results (Fig. 5.1h) for the nitration reaction of toluene and *t*-butylbenzene clearly indicate that alkyl groups are ortho-para directors, the combination of ortho- and para-products account for at least 90% of the products for both reactions. Comparing the two reactions further, however, we will see the different ortho/para product ratios. For toluene, substituent CH_3 is a small size group, the ortho/para ratio is about 2:1, and it matches the statistical ratio

of ortho and para positions. When the size of the substituent increases to t-butyl, para-product is the major one. The steric effect can explain this, that the ortho position is less favorable because of the steric hindrance for the bulky t-butyl group. Usually, the bulky alkyl group can be regarded as a para director predominantly.

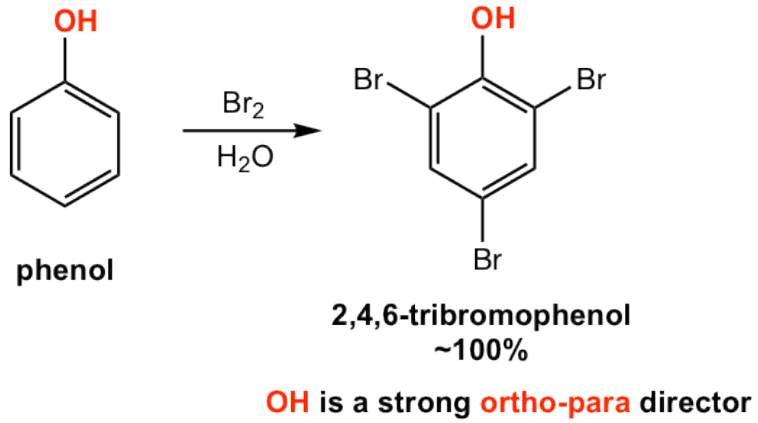


Fig. 5.2d Bromination reaction of phenol

The reaction condition and result of the bromination of phenol (Fig. 5.2d) might be surprising to us. Lewis acid catalyst, for example, $FeBr_3$, is usually required for bromination. However, no catalyst is required for the bromination of phenol, the reaction occurs readily in a bromine solution, with 2,4,6-tribromophenol obtained as a product. All the ortho and para positions are brominated in the product. This result indicates that OH is a strong activating group and strong ortho-para director. Generally, substituents with lone pair electrons on the atom adjacent to the benzene ring, for example, -OH, -OR, $-NH_3$, $-NH_2R$, are stronger activating groups than groups without lone pair electrons (like the alkyl group), and these strong activating groups are strong ortho-para directors.

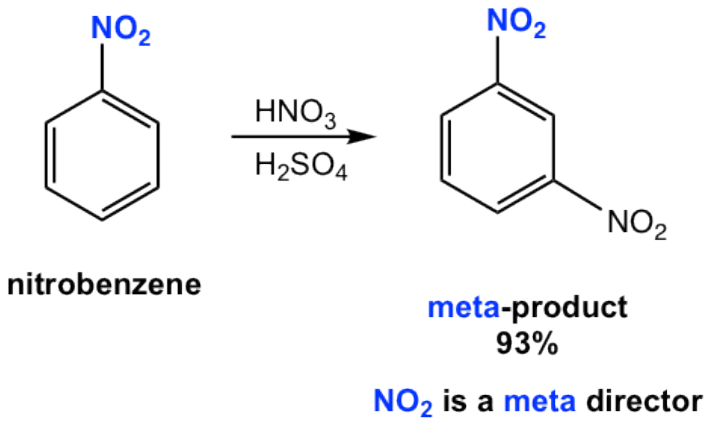


Fig. 5.2e Nitration reaction of nitrobenzene

The Nitro group is a strong deactivating group, with a reaction rate about 1/10000 times that of benzene. Most deactivating groups are meta directors, and the nitration of nitrobenzene takes place in the meta position with a 93% yield (Fig. 5.2e).

5.2.2 Unique Halogen Substituent: Deactivating Ortho-Para Director

Halogen substituents (Cl, Br, and I) affect the EAS in a rather unique way. Halobenzene undergoes aromatic substitution much slower than benzene, which indicates halogen is the deactivating group. However, the incoming group is oriented on ortho- and para-positions predominantly, as the reaction results of chlorobenzene shown in Fig. 5.2f. The halogen substituent is therefore a deactivating ortho-para director.

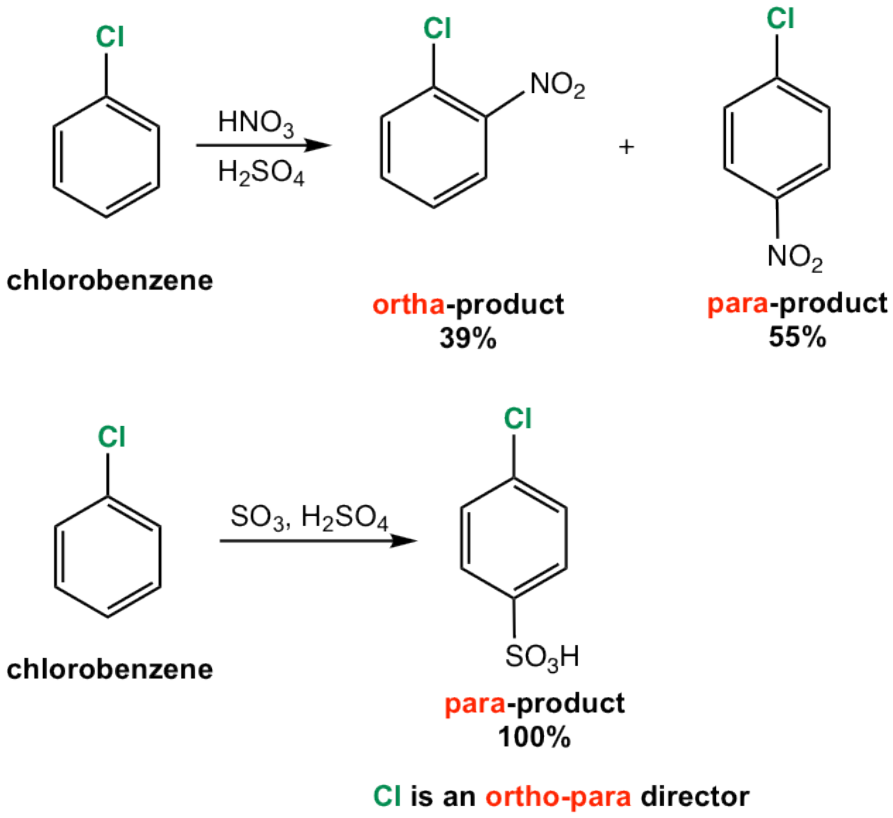


Fig. 5.2f Nitration and sulfonation reaction of chlorobenzene

In summary, different substituents can be classified into several categories, depending on the directing effect, and the strength of activating/deactivating ability, which is shown in **Table 5.1**.

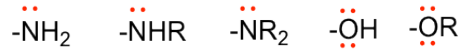
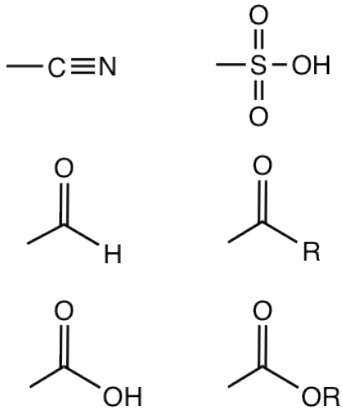
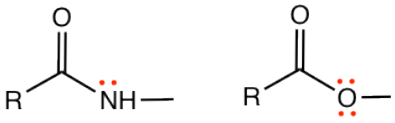
Ortho-para directors	Meta directors
strongly activating 	**strongly deactivating** $-NO_2$, $-NH_3^+$, $-NR_3^+$, $-CF_3$ **moderately deactivating** 
moderately activating 	
weakly activating -R (alkyl), -Ar (aryl)	
weakly deactivating -F, -Cl, -Br, -I	

Table 5.1 Effect of substituents on EAS reaction

Notes for Table 5.1:

- Substituents with lone-pair electrons on the atom bonded directly on the benzene ring, such as -OH, -OR, $-NH_3$, $-NH_2R$, etc, are strong activating groups and strong ortho-para directors.
- Substituents containing multiple bonds besides the atom with lone-pair electrons are moderate activating groups. The electron-withdrawing effect of the multiple bonds weakens the electron-donating effect of the lone-pair electron. Examples include -OCOR, -NHCOR.
- Alkyl groups (no lone pair electrons) are weak activating groups.
- Halogens are weakly deactivating groups, but ortho-para directors.
- Substituents with heteroatoms (N, O, etc) that **don't** have lone-pair electrons, for example, NH_3^+, only the inductive electron-withdrawing effect applies because of the high electronegativity of the heteroatom, these substituents are strong deactivating groups.
- Substituents with multiple bonds connected directly on the benzene ring, for example, -COR, -COOR, -C≡N, are generally moderate deactivating groups.

5.2.3 Explanation of Directing (Orientation) Effect: Understand the Reasons Behind

Ortho-para Directors

The directing effect of a substituent can be explained from two perspectives.

The first explanation focuses on how the substituent affects the electron density of the benzene ring, and it is a more straightforward way to understand. For the electron-donating group, such as -OH, the electron density is transferred to the benzene ring via the resonance effect. From the resonance structures shown below in Fig. 5.2g, it is clear that the extra electron density is localized on the **ortho and para** carbons, therefore these carbons are more likely to react with the electrophile.

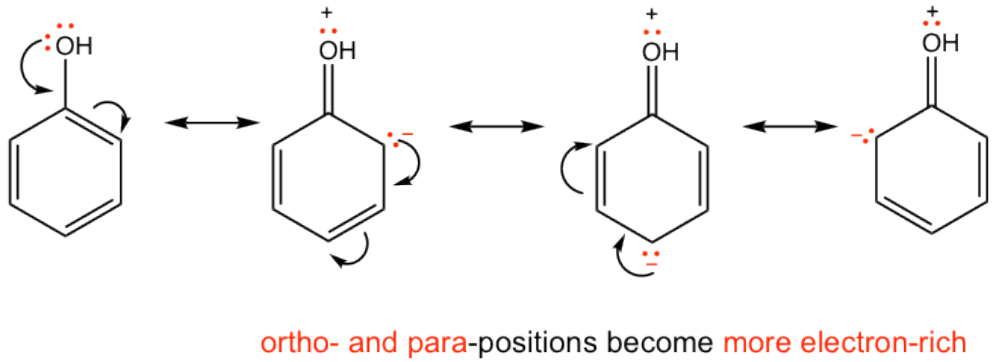


Fig. 5.2g Electron density changes on benzene ring caused by OH group

The second way of explanation relies on the stability comparison of the arenium ion intermediates, that would arise from the attack on different positions.

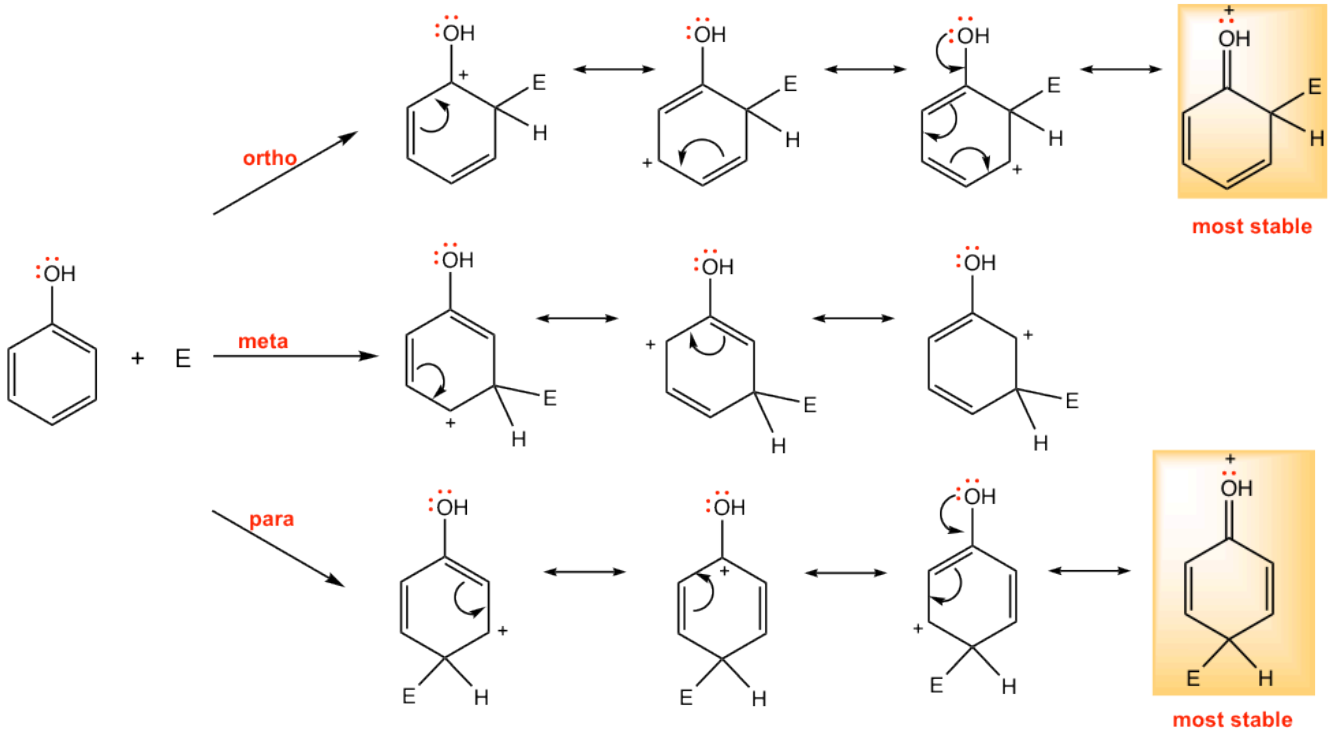


Fig. 5.2h Resonance structures of arenium ion intermediate for electrophilic attack of phenol at different positions

For ortho and para attacks of phenol, there are ***four*** resonance structures available for the arenium ion, and one of them shows special stability with all atoms having complete octets (Fig. 5.2h). Because of the special stability of this resonance structure, it makes a large contribution to the hybrid structure, and stabilizes the arenium ion significantly. For meta attack, however, only ***three*** resonance structures are available, and none of the resonance structures has all complete octets. These observations suggest that the ortho- and para-substituted arenium ions are considerably more stable than those from the meta attack, as a result, these are the preferred pathway for the reaction.

Meta Directors

Most deactivating groups are meta directors, this can also be explained by two perspectives. Only the first way is shown here to simplify the process.

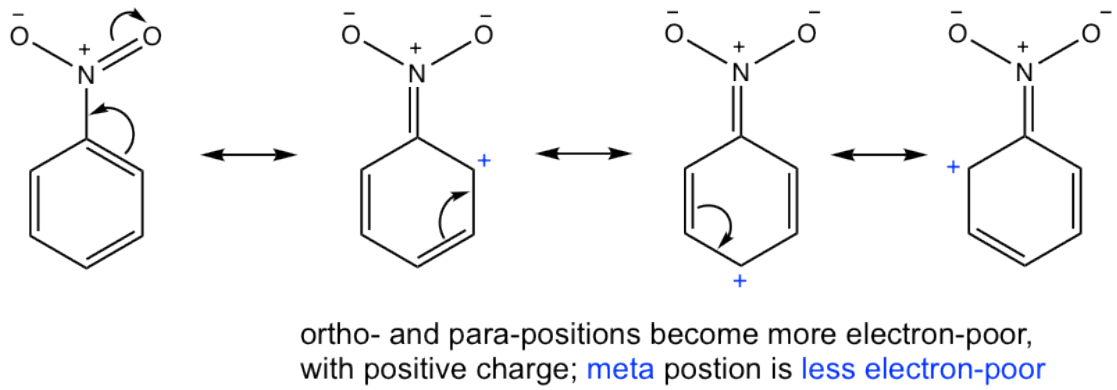


Fig. 5.2i Electron density changes on benzene ring caused by NO2 group

The electron-withdrawing effect via resonance makes the ortho- and para-positions most electron-poor, therefore meta position is a "better" choice for electrophilic attack since it is relatively more electron-rich than ortho and para positions.

Understand the Unusual Halogens

Although most deactivating groups are meta directors, halogens are different. Halogens are weakly deactivating groups, however, they are also ortho-para directors. The seems contradictory behavior can be explained that the **reactivity of halobenzene is affected by the electron-withdrawing inductive effect** (because of the electronegativity of halogen), **and the orientation effect is determined by the electron-donating resonance effect** (by lone pair electrons on halogen).

The electron-donating via resonance effect requires orbital overlapping between halogen and carbon on the benzene ring. The relatively large size of halogens (Cl, Br, and I) makes such overlapping less effective, so the inductive effect wins over the resonance effect for changing the electron density on the benzene ring. The halobenzene is slightly more electron-poor than benzene, so the halogen substituent is the weakly deactivating group.

The orientation effect of halogen can be explained through the different stability of arenium ions by the attack on different positions, in a similar way as for the OH group.

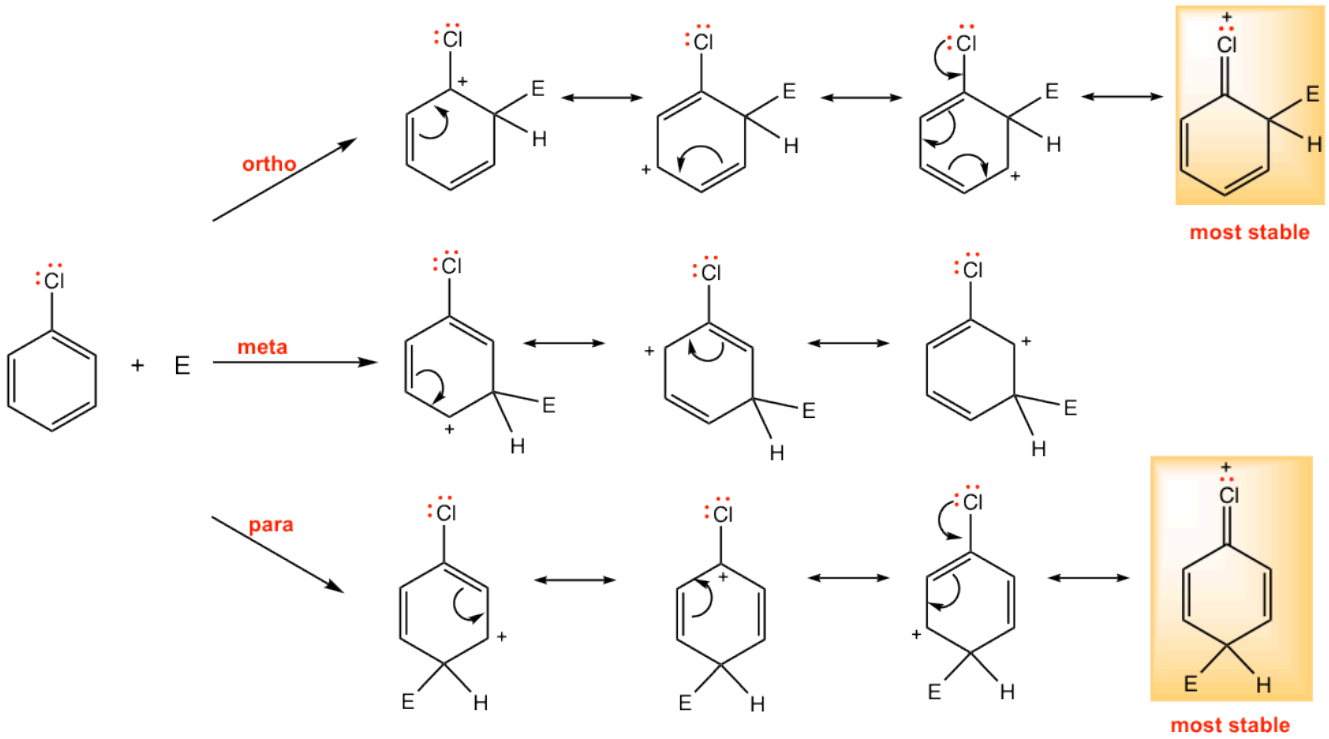


Fig. 5.2j Resonance structures of arenium ion intermediate for electrophilic attack of chlorobenzene at different positions

As shown in Fig. 5.2j, for chlorobenzene, there is one more resonance structure with a complete octet available for the arenium ion intermediate in ortho and para attack, the arenium ion is stabilized significantly. For meta attack, however, only *three* resonance structures are available, and none of the resonance structures has all complete octets. Therefore the ortho- and para-substituted arenium ions are considerably more stable than those from the meta attack, and these are the preferred pathways for the reaction.

5.3 EAS on Di- or Tri-substituted Benzenes

For EAS reaction on disubstituted benzene, the directing effects of both substituents have to be considered.

When both substituents direct the incoming reaction onto the same position, it is easy to predict the product, as in the example given below for o-hydroxybenzoic acid (Fig. 5.3a). The ortho and para position of the OH group is also the meta position of the COOH group, so the EAS of o-hydroxybenzoic acid occurs on the positions with orange arrows.

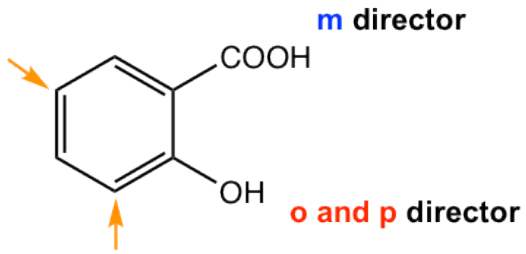


Fig. 5.3a The position of incoming EAS for o-hydroxybenzoic acid

If the two substituents direct the incoming reaction on different positions, a stronger activating substituent wins out over a weak activating or a deactivating group.

For the case of p-methylphenol (Fig. 5.3b), the ortho position of OH is the meta position of CH_3. Since OH is the stronger activating group, it determines the position in which the coming EAS takes place, that is the position with the orange arrow.

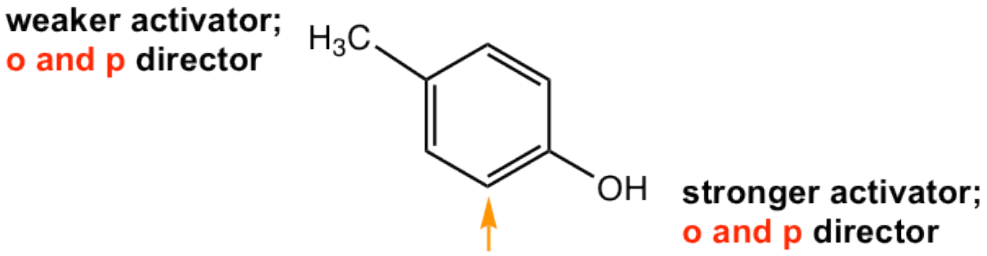


Fig. 5.3b The position of incoming EAS for p-methylphenol

The above guidelines also apply to tri-substituted benzenes.

5.4 Synthesis of Benzene Derivatives

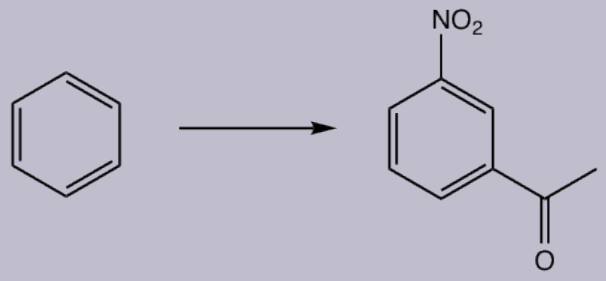
5.4.1 Applications of EAS in Synthesis

EAS reaction on benzene is a powerful tool in the synthesis of benzene derivatives with a variety of structures. In planning the synthesis route, some considerations need to be accounted for.

- Looking at the activating/directing effects of substituents, to decide the proper order for carrying out the different EAS reactions, as in the example given below.

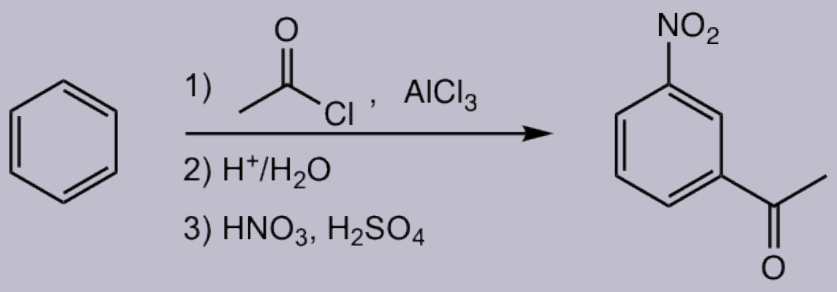
Examples

Propose a synthesis route for the following benzene derivative.



To synthesize the target compound, it seems that does not matter to introduce which group first since both NO_2 and $COCH_3$ are m-directors. A further look, however, indicates that NO_2 is a strong deactivating group and makes the second EAS reaction much more difficult. So it is more reasonable to do Friedel-Drafts acylation first, then nitration.

Answer:



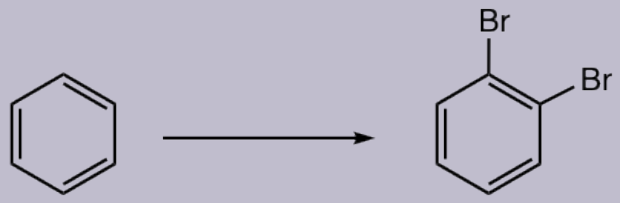
- Consider the reactivity and/or side reactions, for example, the limitations for Friedel-Crafts alkylation.

Refer to the example given in **section 4.7.3**.

- To synthesize the sterically hindered isomer, apply the blocking/deblocking strategy, as in the example given below.

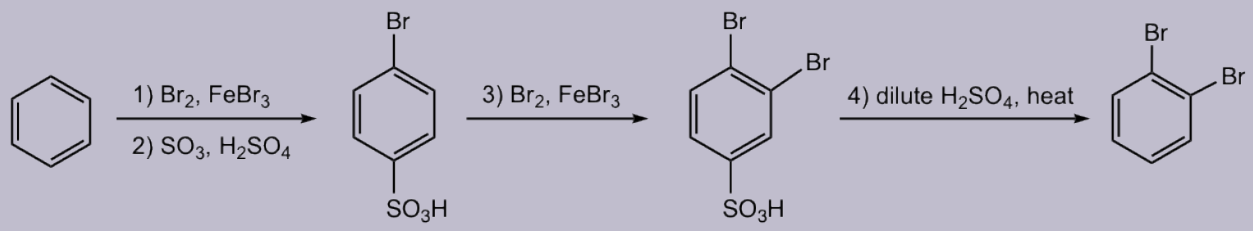
Examples

Propose a synthesis route for the following benzene derivative.



Bromine is an ortho-para director. When the 2nd bromination occurs, the 2nd Br atom goes to both ortho- and para-positions, with para-isomer slightly favored because of the steric hindrance on ortho-position. How to synthesize the o-dibromobenzene exclusively, without getting p-dibromobenzene? The strategy of introducing -SO_3H as a blocking group is what can be applied for such a purpose.

Answer:



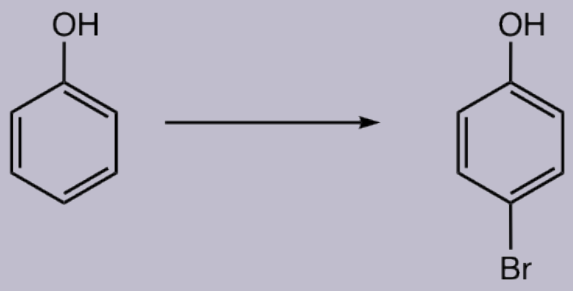
The sulfonation of bromobenzene occurs only on the para-position, because of the large size of the SO_3H group. Since the SO_3H group blocks the para-position of bromobenzene, the 2nd Br group will be introduced to ortho-position exclusively. The final product is obtained by the removal of the blocking group SO_3H by heating in an acidic solution.

- Convert a strong activating group to a milder one, as in the example given below.

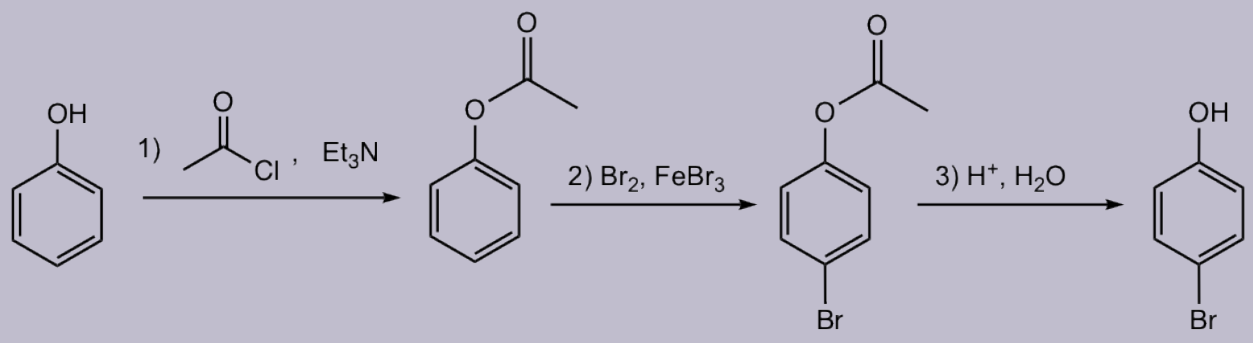
As mentioned in **section 5.1.2**, direct bromination of phenol results in 2,4,6-tribromophenol because of the strong activating property of the OH group. To avoid the undesired reactions, the strong activating groups such as OH or NH_2 can be converted to a milder activating group, such as ester (OCOR) or amide (NHCOR) respectively. At the end of the reaction, these groups will be converted back to the original version.

Examples

Propose a synthesis route for the following benzene derivative.



Answer:



The reactions for preparing ester from alcohol, and the hydrolysis of ester to alcohol will be discussed in detail in Chapter 7.

5.4.2 Reaction of the Alkyl Substituents on Benzene Derivatives for Alkylbenzenes

Other than the EAS reactions, the conversions of substituents on the benzene ring to other functional groups also help to expand the scope for the synthesis of benzene derivatives. The reactions of the alkyl substituents of alkylbenzene will be summarized here. You will find that some of the following examples involve the reactions we have learned in earlier chapters, and a few brand-new reactions will be added.

Halogenation of the Alkyl substituent for Alkylbenzene (Radical)

Radical halogenation takes place on alkane, so it also occurs on the alkyl substituent on alkylbenzene. The benzylic position is the first choice for this reaction because of the special stability of the benzylic radical (refer to **section 9.3 in Book I**, and **section 3.2**).

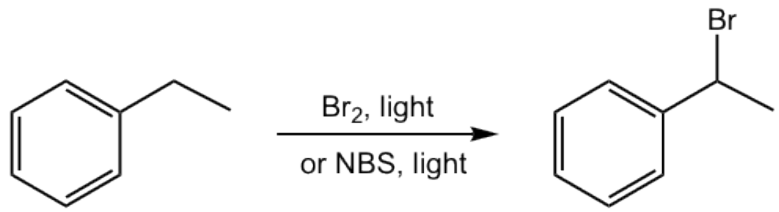


Fig. 5.4a Benzylic bromination of alkylbenzene

Once the halogen is introduced into the alkyl substituent, the benzylic halide could undergo substitution or elimination as other halides, examples are given in Fig. 5.4b.

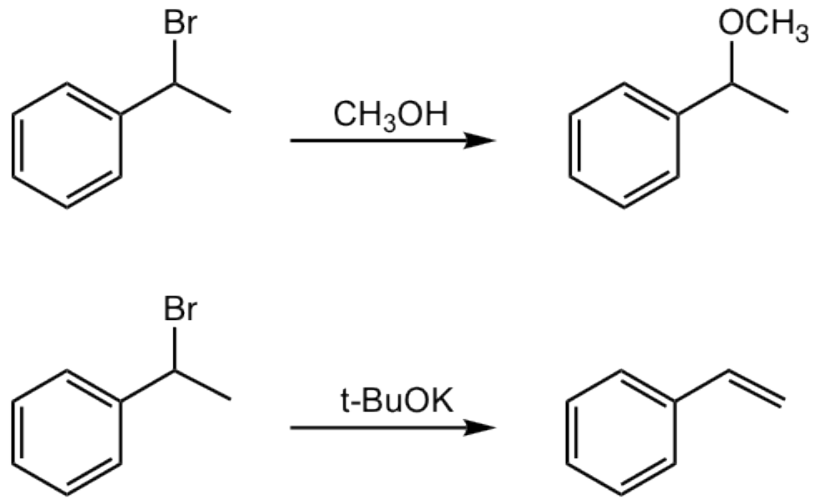


Fig. 5.4b Further reactions of benzylic bromide

Oxidation of the Alkyl substituent for Alkylbenzene

The alkyl substituent on alkylbenzene can be oxidized by a strong oxidizing agent to a carboxylic acid (COOH) group. Two strong oxidizing agents can be used for this reaction: $KMnO_4$ in basic condition, or $Na_2Cr_2O_7$ in acidic solutions.

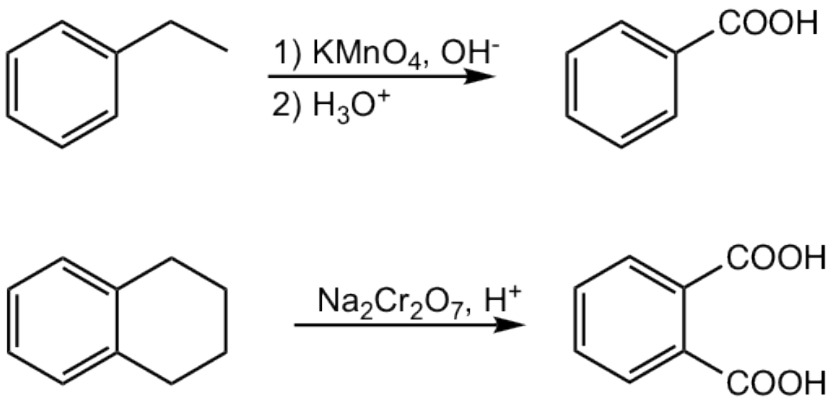


Fig. 5.4c Oxidation of the alkyl substituent for alkylbenzene

The initial step of the reaction is that the oxidizing agent abstracts a benzylic hydrogen, therefore only the alkyl group with the hydrogen on the benzylic position undergoes the oxidation.

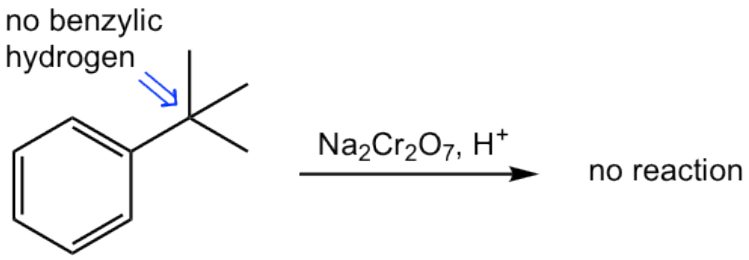


Fig. 5.4d Tertiary group on alkylbenzene does not undergo oxidation

Conversion of NO_2 to NH_2 group

As we will learn in the next **section 5.5**, aniline is an important benzene derivative that has special application in synthesis. However, the NH_2 group cannot be introduced to the benzene ring directly. Instead, aniline can be prepared by reduction of nitrobenzene.

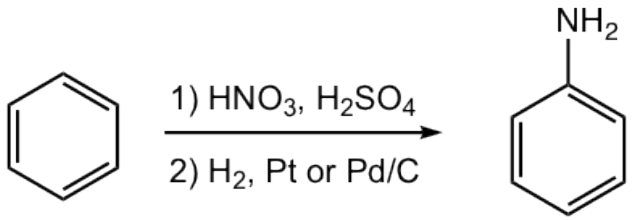


Fig. 5.4e Preparation of aniline from benzene

5.5 Arenediazonium Salt

Preparation and Structure of Arenediazonium Salt

Aniline can be converted to arenediazonium salt by reaction with nitrous acid (HNO_2). The arenediazonium salt can undergo further substitution and coupling reactions which are important methods to produce more benzene derivatives.

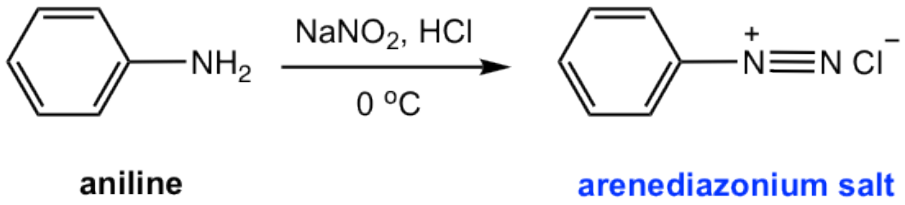


Fig. 5.5a Preparation of arenediazonium salt from aniline

When treated with nitrous acid (HNO_2) at 0 °C, the NH_2 group on aniline is converted to the arenediazonium salt.

Nitrous acid is an unstable acid that has to be prepared *in situ*, by treatment of sodium nitrate ($NaNO_2$) with strong acid solution (HCl), and the reaction system needs to be kept at 0 °C. The diazonium ion then generated can be readily replaced by a variety of nucleophiles (as shown in Fig. 5.5b and Fig. 5.5d), with the formation of nitrogen gas, a stable molecule, which acts as a driving force to facilitate the reaction. The nucleophile reagent can be simply added to the mixture, with no separation of diazonium salt necessary.

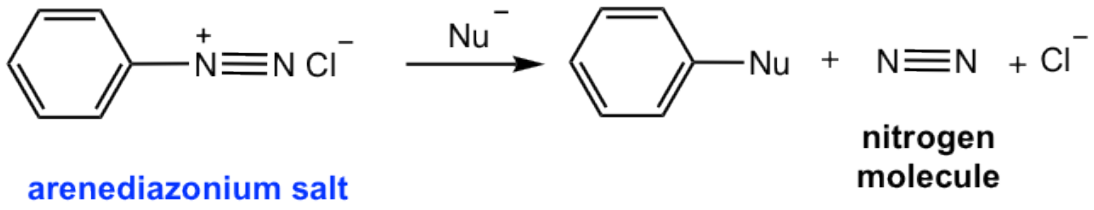


Fig. 5.5b Substitution reaction of arenediazonium salt

As a reactive intermediate, arenediazonium ion is relatively more stable than alkanediazonium because of the resonance effect from the benzene ring. As shown in Fig. 5.5c, multiple resonance structures are available for arenediazonium ion.

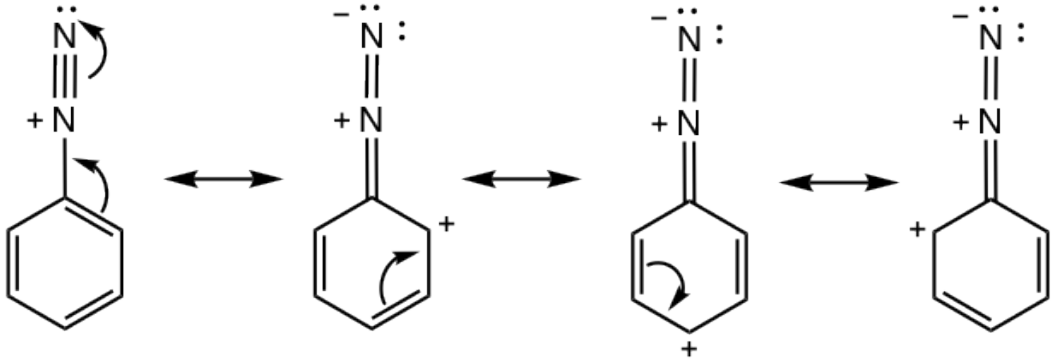


Fig. 5.5c Resonance structures of arenediazonium ion

Syntheses of Substituted Benzene by Using Arenediazonium Salt

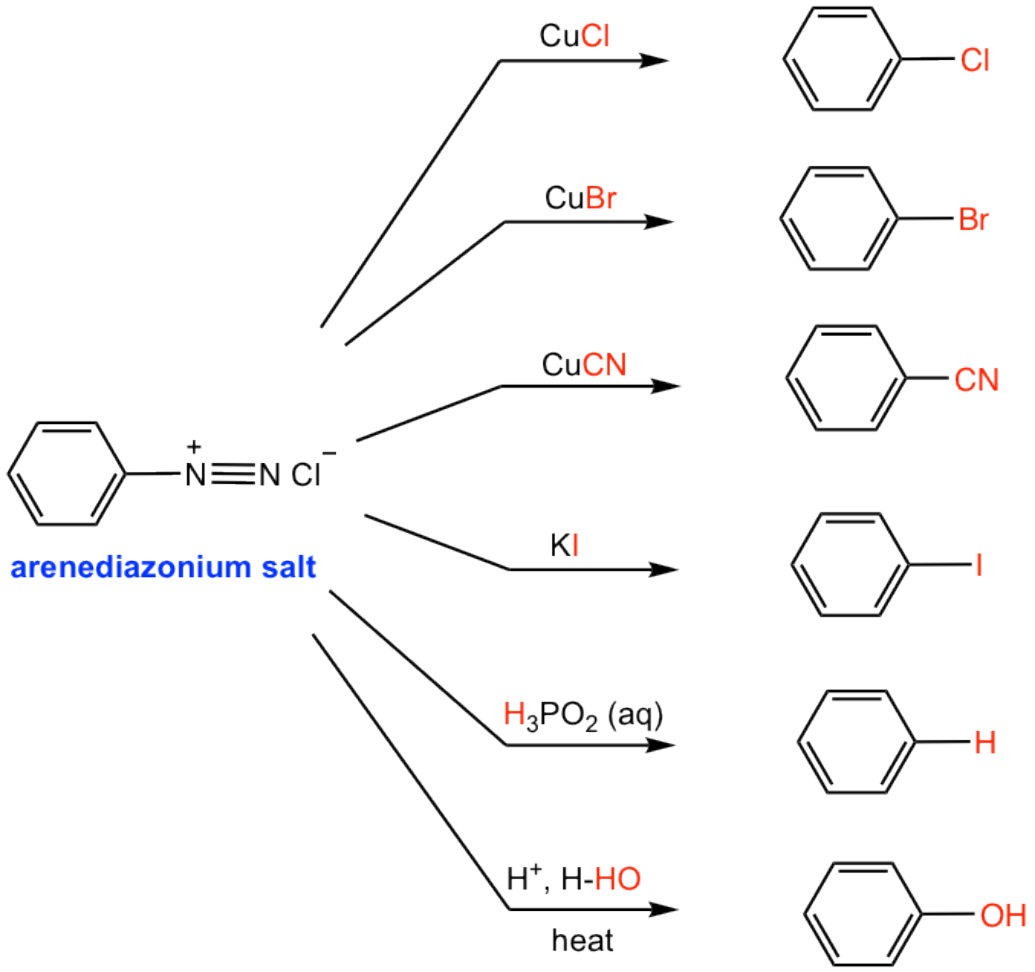


Fig. 5.5d Substitution reactions of arenediazonium salt

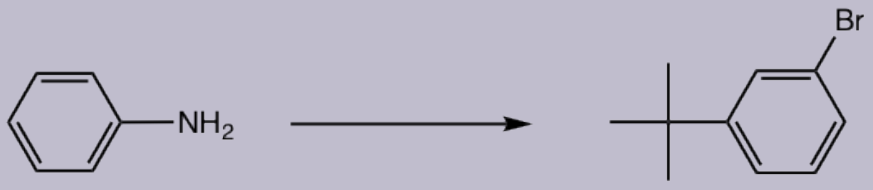
Arenediazonium salt undergoes a series of substitution reactions, with a variety of substituted benzene generated as products (Fig. 5.5d). The reactions of several copper (I) salts, for example, CuCl, CuBr, and CuCN, with arenediazonium salt are generally known as **Sandmeyer reactions**. The diazonium group is replaced by -Cl, -Br, and -CN respectively in these reactions.

To prepare the iodobenzene from arenediazonium salt, potassium iodide (KI) is required.

A useful reaction in synthesis is the replacement of diazonium salt with the hydrogen atom, which is also called deamination (removal of the nitrogen group). This can be achieved by treatment of arenediazonium salt solution with hypophosphorous acid (H_3PO_2) aqueous solution (the 2nd last reaction in Fig. 5.5d). This reaction is useful if the $-NH_2$ group (or the $-NO_2$ group, the precursor of $-NH_2$) is needed for directing purposes, and must be removed afterward. Such application is illustrated in the following synthesis example.

Examples

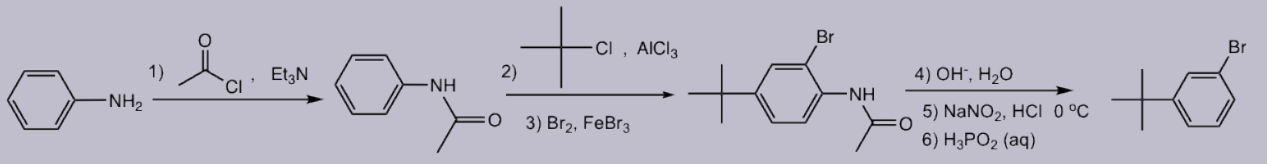
Design the synthesis of *m*-bromo-t-butylbenzene from aniline.



Approach:

- NH_2 is first converted to NHCOR, a milder activator and also ortho-para director;
- t-Butyl group is then introduced by Friedel-Crafts alkylation, the para isomer will be obtained as a major product because of steric effect;
- Br is introduced next by bromination;
- NHCOR is hydrolyzed back to the NH_2 group, which is converted to diazonium salt, and then replaced by H.

Answer:



If the acidic solution containing arenediazonium salt is warmed up, the -OH group will replace the diazonium salt in which H_2O acts as the nucleophile (the last reaction in Fig. 5.4d). This is a method to prepare phenol from aniline.

Another better alternative to preparing phenol (Fig. 5.5e) is to add copper(I) oxide and copper(II) nitrate to the cold solution of arenediazonium salt. The diazonium salt is replaced by the -OH group in such conditions without heating.

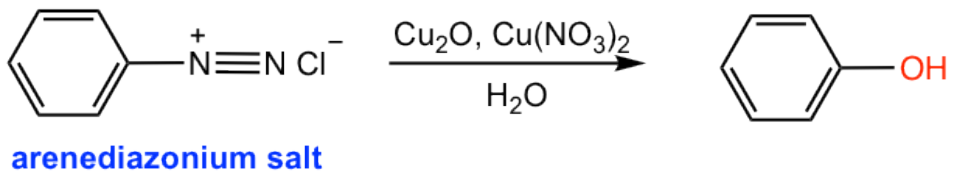


Fig. 5.5e Alternative way of converting arenediazonium salt to phenol

Coupling Reaction of Arenediazonium Salt

The arenediazonium salt can also react as an electrophile in the electrophilic aromatic substitution (EAS) reaction. Since arenediazonium salts are weak electrophiles, highly activated aromatic compounds, such as phenol or aniline, are required. The product of such a reaction contains an N=N linkage structure unit. The N=N is called an azo linkage, and the product is called the **azo compound**. The azo compound comes from the connection of arenediazonium salt with an aromatic compound, so the reaction is also called the coupling reaction. Because of the relatively large size of the arenediazonium salt, the EAS reaction usually takes place at the para position due to steric hindrance.

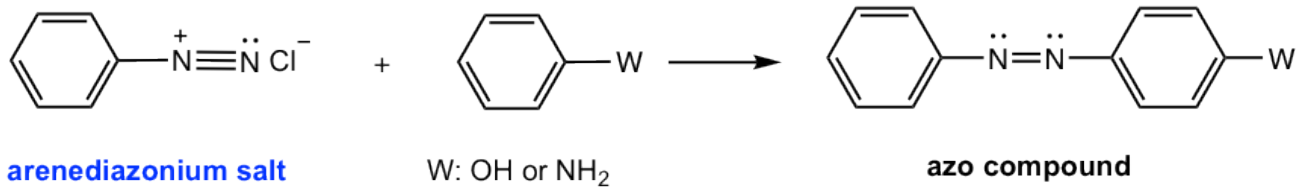


Fig. 5.5f General equation of coupling reaction of arenediazonium salt

The mechanism for the coupling reaction (Fig. 5.5g) still follows the general mechanism of EAS, in which two steps are involved: the arenediazonium salt attacks the benzene ring as an electrophile, then deprotonation.

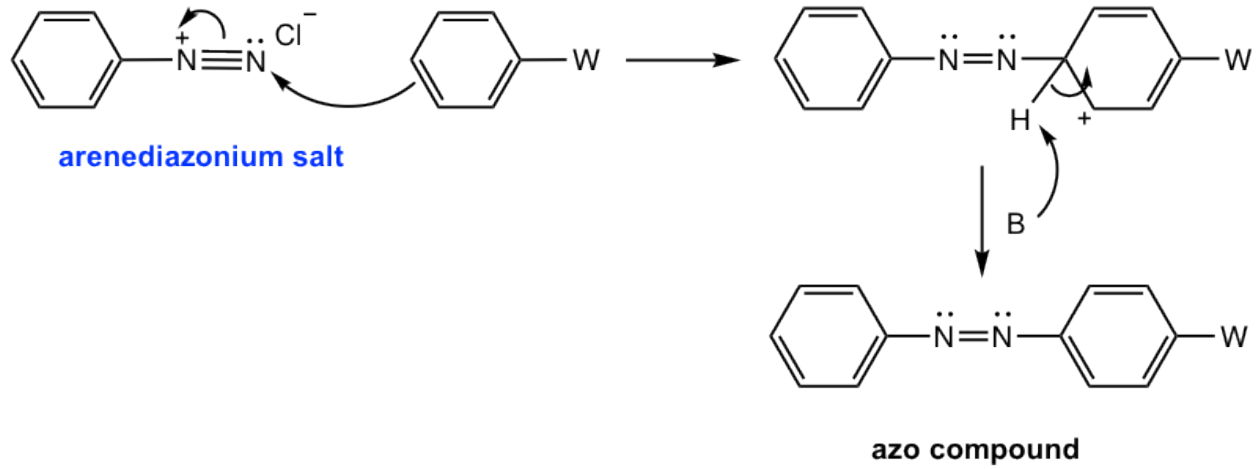


Fig. 5.5g Mechanism for coupling reaction of arenediazonium salt

Reactions between arenediazonium salt and phenols are usually carried in a slightly alkaline solution. Phenol is present as phenoxide ArO^- in such conditions, which is more electron-rich than phenol itself and more reactive towards EAS.

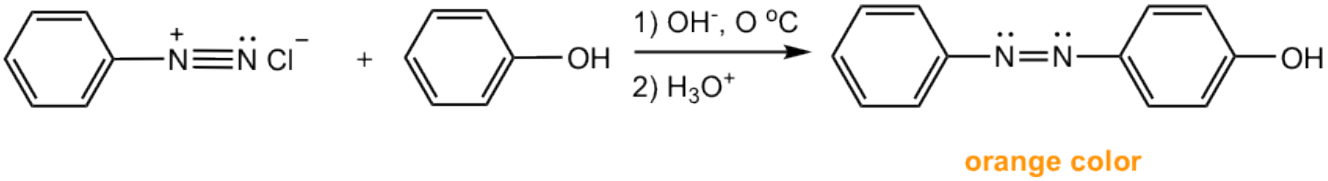


Fig. 5.5h Reaction of arenediazonium salt with phenol

When arenediazonium salt reacts with aniline (or another aromatic amine), the reaction condition should be controlled as slightly acidic (pH 5 ~ 7). This is because that aniline will be protonated to unreactive aminium salt under a strong acidic condition and arenediazonium salt loses its reactivity in a strong basic condition.

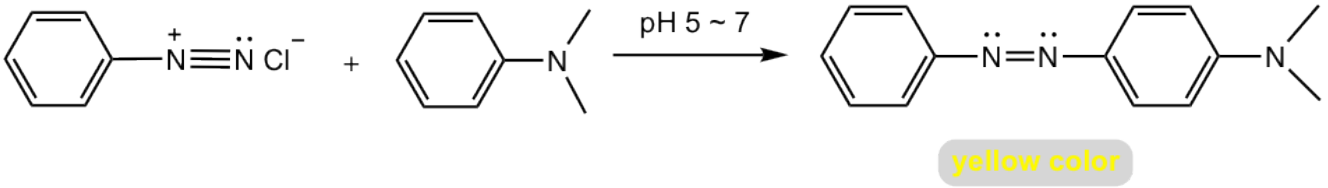


Fig. 5.5i Reaction of arenediazonium salt with aniline

The azo linkage connects the two aromatic rings into an extended conjugation system, therefore azo compounds are usually intensely colored and are used as synthetic dyestuffs that are referred to as azo dyes. The product of the reaction in Fig. 5.4h used to be employed as a food dye called butter yellow.

5.6 Nucleophilic Aromatic Substitution: SNAr

The keyword for the reactions of aromatic systems we learned so far is **electrophilic substitution**. Here we will explore the possibility of **nucleophilic substitution** of aromatic compounds.

5.6.1 Nucleophilic Aromatic Substitution by Addition-Elimination (S_NAr)

When we learned about nucleophilic substitution (S_N1 or S_N2), we saw that these reactions generally don't apply to aryl halide.

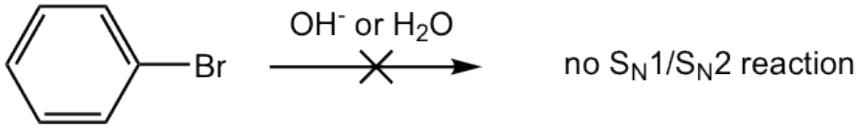


Fig 5.6a No S_N1/S_N2 reaction on aryl halide

However, when there are one or more **electron-withdrawing substituents** present on aryl halide, it **does** undergo nucleophilic substitution, which involves the **addition-elimination** mechanism.

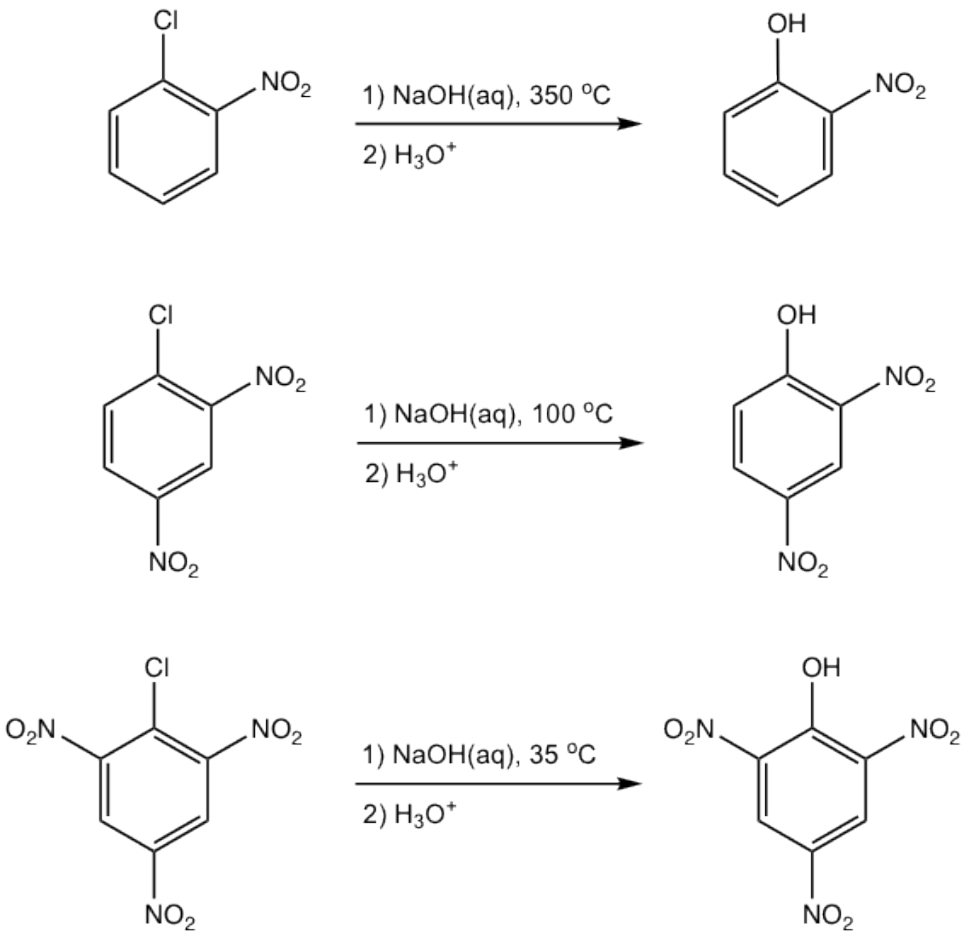


Fig. 5.6b Nucleophilic substitution reaction of nitro-substituted chlorobenzenes

It is noticed from the above examples that the greater the number of electron-withdrawing substituents present, the more easily the nucleophilic aromatic substitution occurs (the lower the reaction temperature). Further studies also indicate that the electron-withdrawing substituent must be on ortho or para position to the halogen, to make the reaction possible. All these observations can be explained by the reaction mechanism that the electron-withdrawing substituents on ortho (or para) positions help to stabilize the carbanion intermediate (Fig. 5.6c).

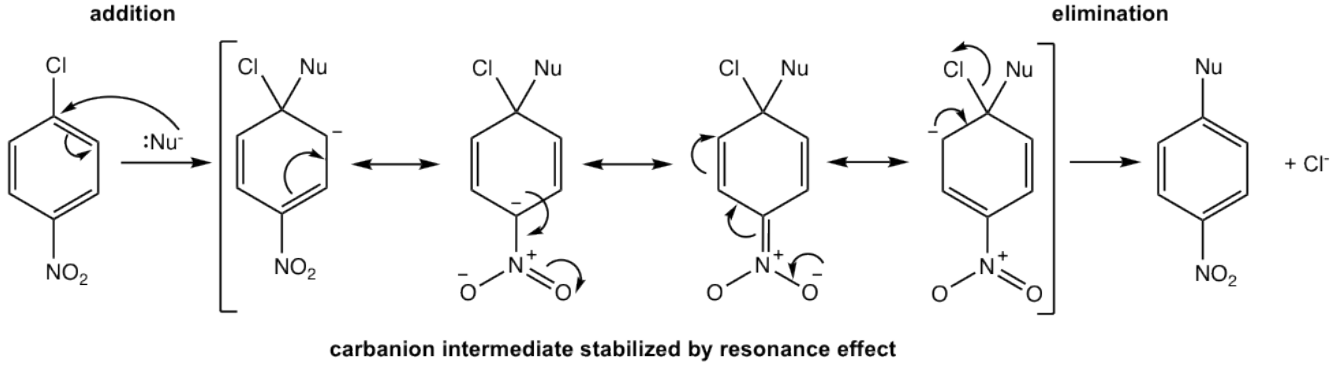


Fig. 5.6c Mechanism for Nucleophilic Aromatic Substitution (S_NAr)

Such a mechanism is for **nucleophilic aromatic substitution**, a two-step process, with the symbol **S_NAr**. In the first step, the nucleophile attacks the carbon attached to the leaving group (halide) and produces the carbanion intermediate. The negative charge of the carbanion can be stabilized via resonance effects of electron-withdrawing groups on ortho (or para) positions, as shown in Fig. 5.6c (only NO_2 in the ortho position is shown as an example). The leaving group, which should also be a weaker base similar to the case in the S_N2 reaction, is then eliminated in the second step, and the aromaticity is restored in the product.

5.6.2 Nucleophilic Aromatic Substitution that Forms a Benzyne Intermediate

Under harsh reaction conditions, aryl halide without electron-withdrawing substituents does react with strong nucleophiles for substitution. For example, when chlorobenzene is heated with NaOH solution at 350 °C, the Cl is replaced by OH, and phenol is obtained as a product.

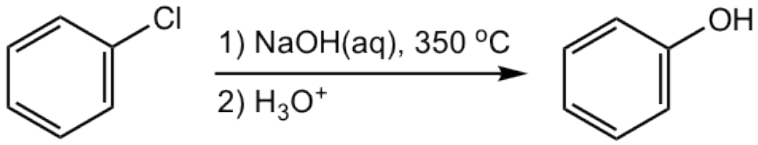


Fig. 5.6d Chlorobenzene converted to phenol via substitution reaction at high temperature

Chlorobenzene also reacts with amide (NH_2^-) and gives aniline product. When C-14 labeled chlorobenzene is treated with amide, half of the product has the amino group attached to the labeled carbon, and the other half has the amino group attached to the adjacent position of the labeled carbon, as shown in Fig. 5.6e. The C-14 labeled carbon is marked * in the reaction equation.

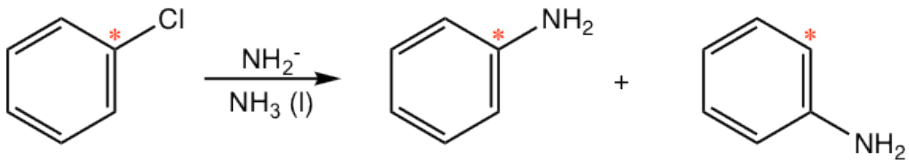


Fig. 5.6e Substitution reaction of isotopically labeled chlorobenzene with amide to aniline

There are two unusual aspects of the above reactions:

- No electron-withdrawing group is present in the aryl halide.
- The amino group is attached to different carbons in the products.

This type of aromatic substitution has a different mechanism than S_NAr (**addition-elimination**). It takes place through an **elimination-addition** mechanism that involves an unusual intermediate called ***benzyne***, as shown in Fig. 5.6f.

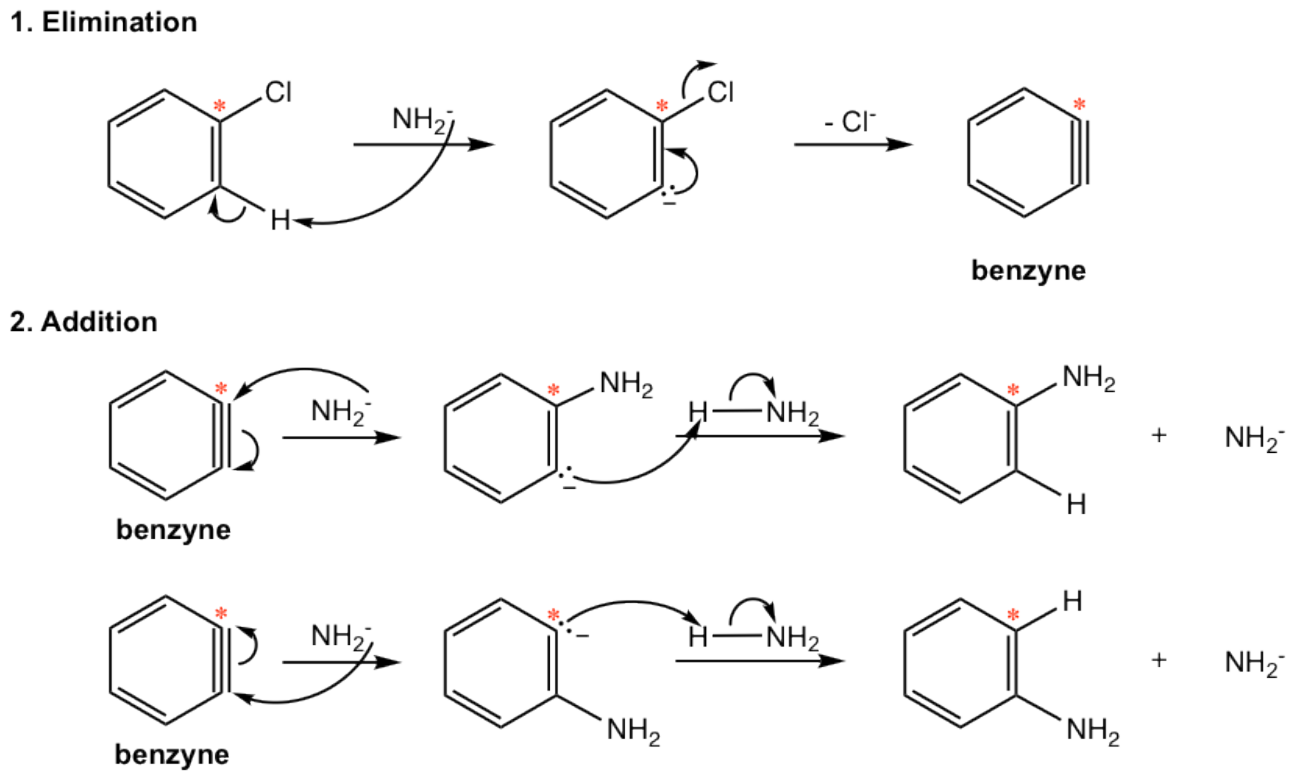


Fig. 5.6f Mechanism for Reaction of Chlorobenzene with Amide (include benzyne)

In the first part of the mechanism, HCl is eliminated and the benzyne intermediate is formed. The elimination of HCl involves two subsequent steps in which the hydrogen on the ortho position of chlorine is first abstracted by an amide ion, to produce the carbon anion, the anion then loses a chloride ion to form benzyne. The reaction of benzyne with nucleophile NH_2^-, followed by a protonation gives the final aniline product. When benzyne reacts with NH_2^-, the attack can occur on either carbon of the "triple bond", which explains the formation of the two "isomers" with the NH_2 group on different carbons.

The Structure and Chemistry of Benzyne

Benzyne is a highly unstable intermediate that has a "triple" bond. Although a triple bond is included in the structure formula of benzyne, it is not a regular triple bond. For a typical triple bond, both carbons are in sp hybridization, and the bond angle is 180°. The carbons in benzyne are in sp^2 hybridization, however, and the bond angles are about 60°. Furthermore, the additional π bond in the benzyne is formed by sp^2-sp^2 overlapping, which is in the same plane of the ring and therefore very weak. As shown in Fig. 5.6g, benzyne is a distorted structure with great electron density on the triple bond edge and therefore is a highly unstable and reactive intermediate.

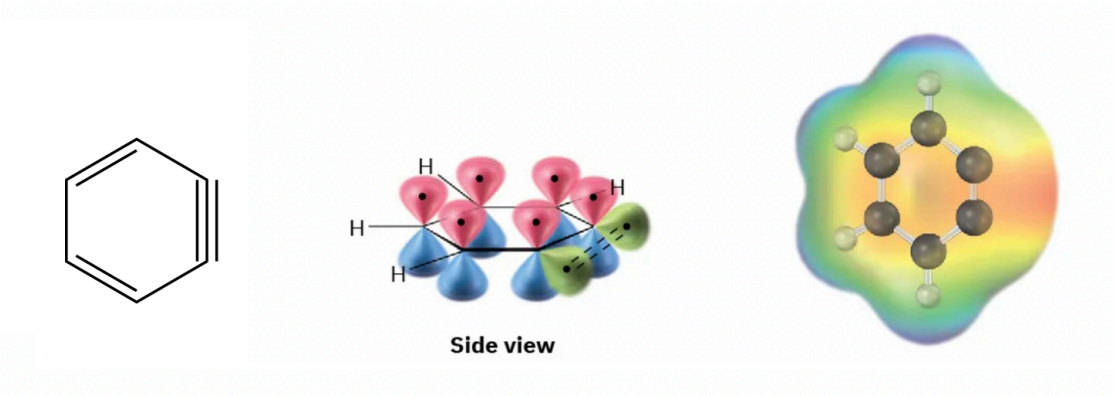


Fig. 5.6g The structure of benzyne: structure formula, side view of orbitals, and electrostatic potential map. This diagram is adapted from the original Libretext, licensed CC BY-NC-SA 4.0 license. This adapted diagram is licensed under the same license.

Benzyne is too unstable to be isolated. Other than the above reaction as evidence for the formation of benzyne intermediate, it can also be "trapped" by reacting with other appropriate reactants. When furan is added to the reaction that forms a benzyne intermediate, the Diels-Alder reaction product can be isolated that comes from the 4+2 addition of furan with benzyne.

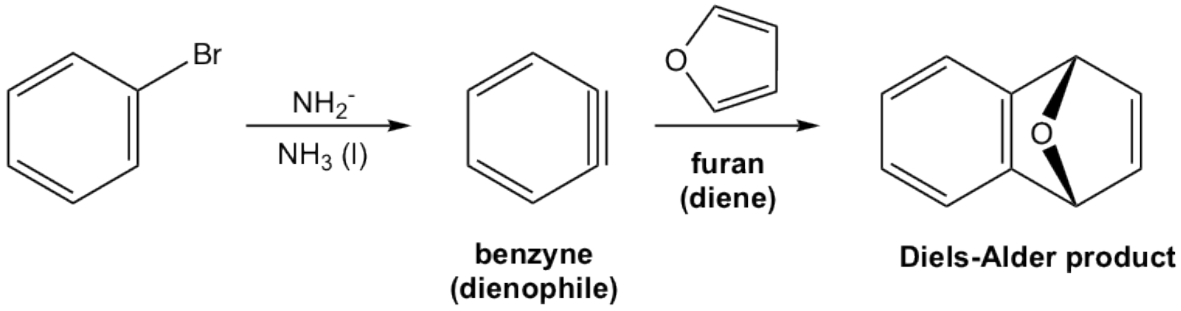
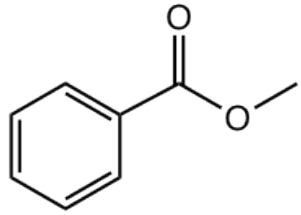
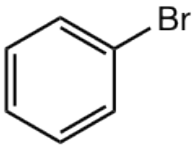
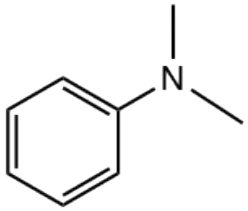


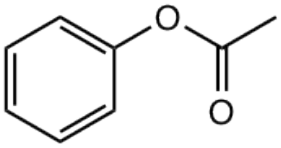
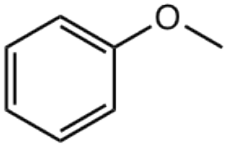
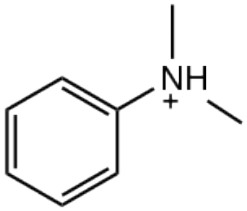
Fig. 5.6h Diels-Alder reaction of benzyne

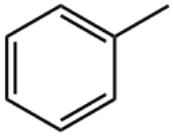
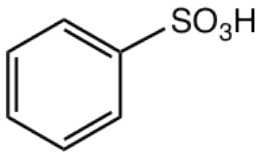
5.7 Practices

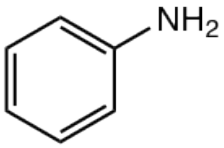
1. Indicate each of the following groups on the benzene ring is an ortho-par or meta director.



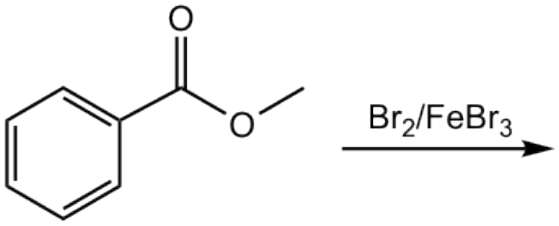






2. Show the major product(s) of the following reactions.

a.



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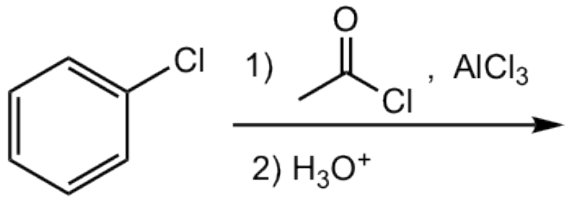

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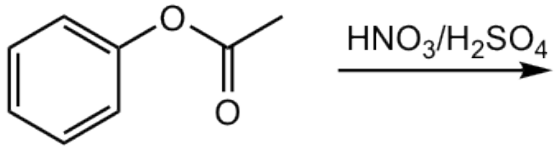

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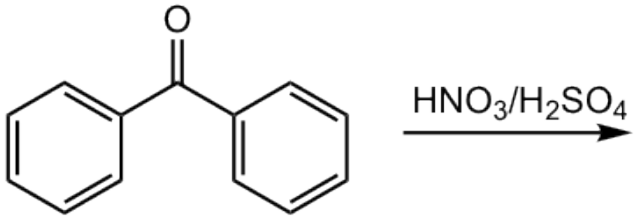

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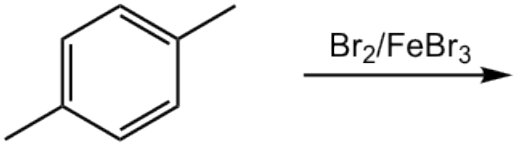
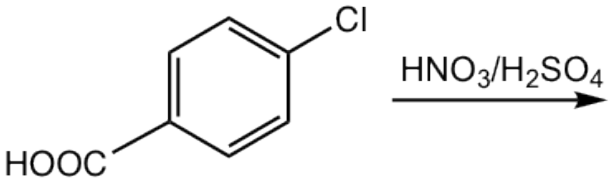
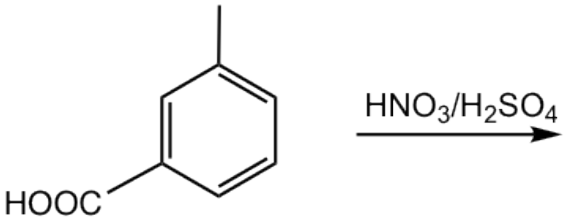


f.



g.



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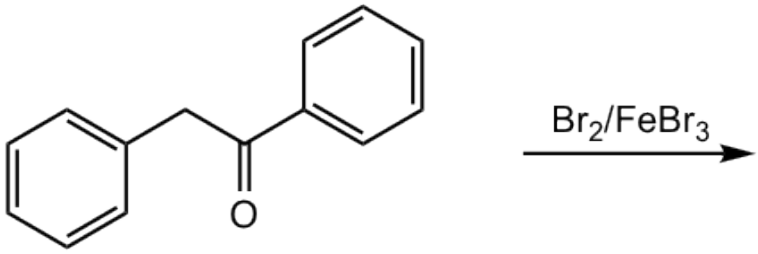
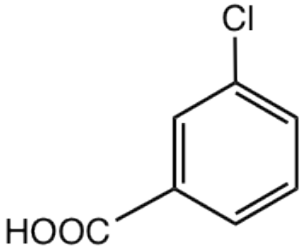
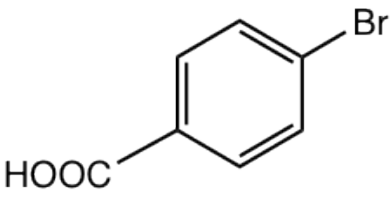
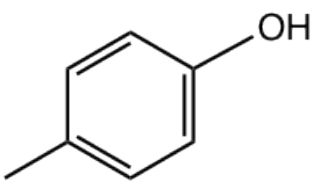


3. Starting with toluene, design the synthesis of each of the following compounds:

a. b. c.

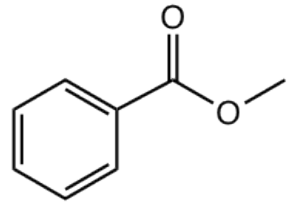




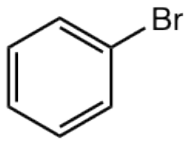


5.8 Practices Answers

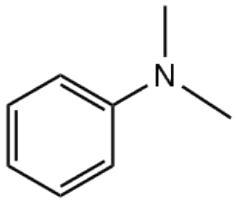
1. Indicate each of the following groups on the benzene ring is an ortho-par or meta director.



meta director



ortho-para director



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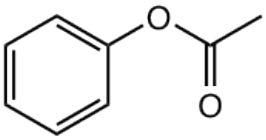

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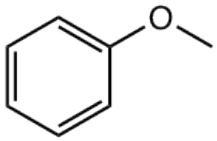

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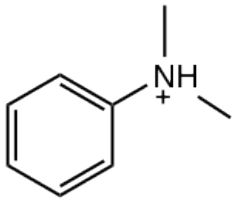

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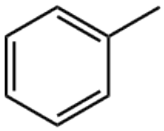

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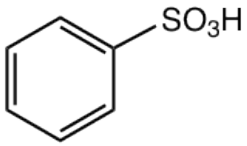
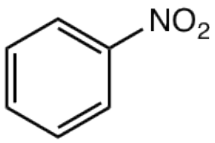


meta director



meta director

2. Show the major product(s) of the following reactions.

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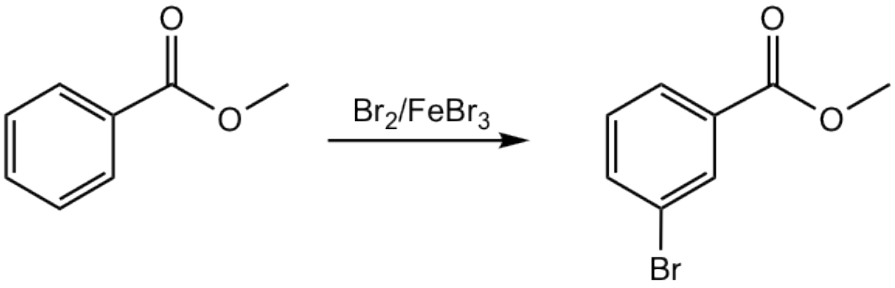
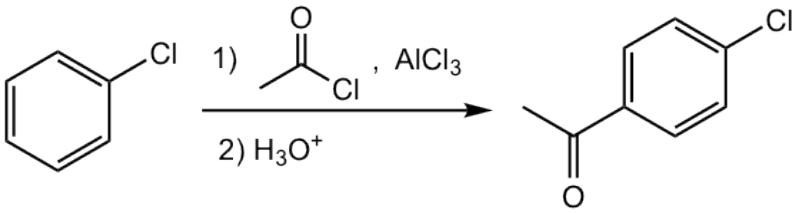
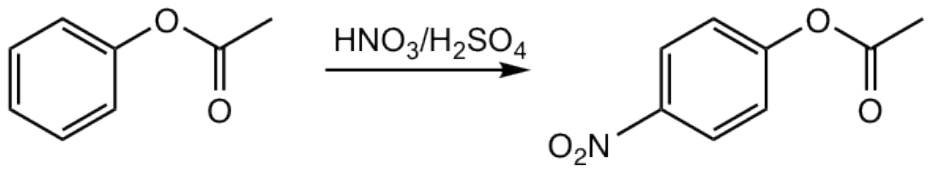


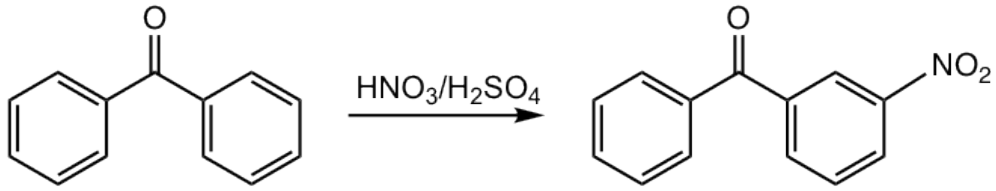
b.



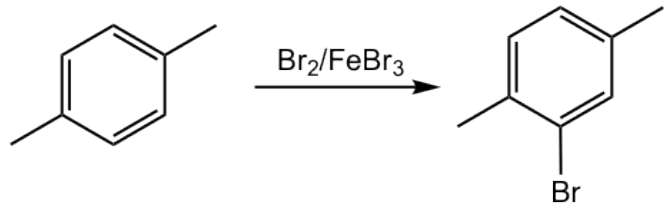
c.



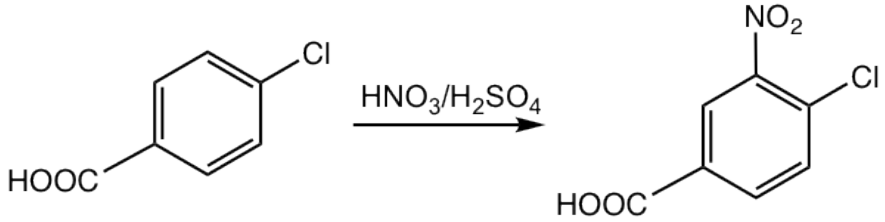
d.



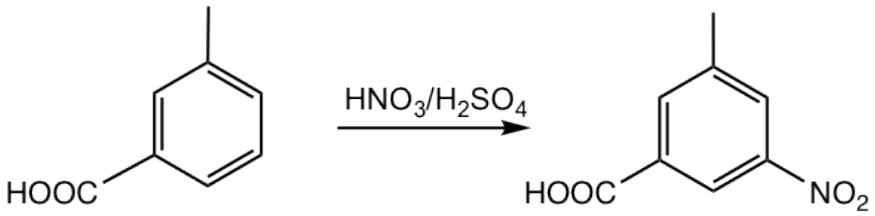
e.



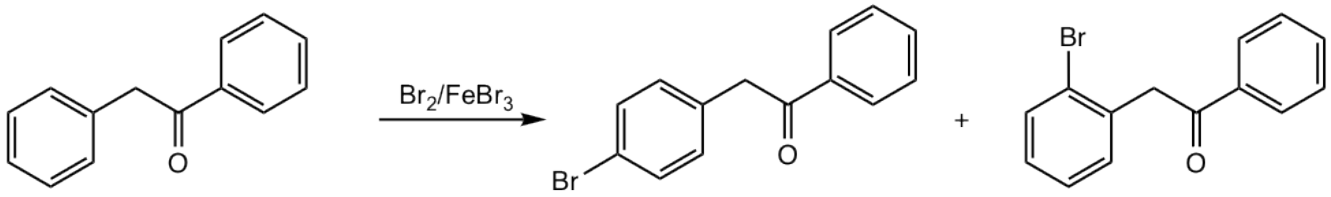
f.



g.

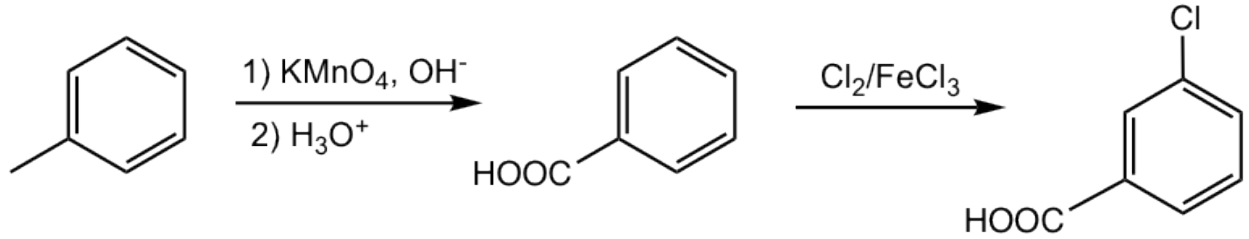


h.

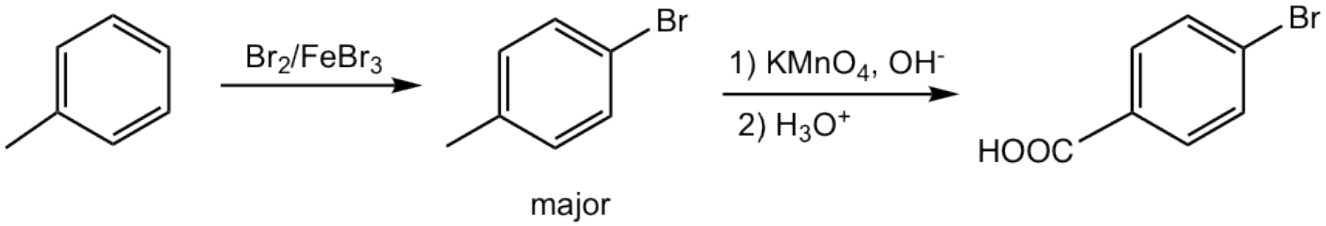


3. Starting with toluene, design the synthesis of each of the following compounds:

a.

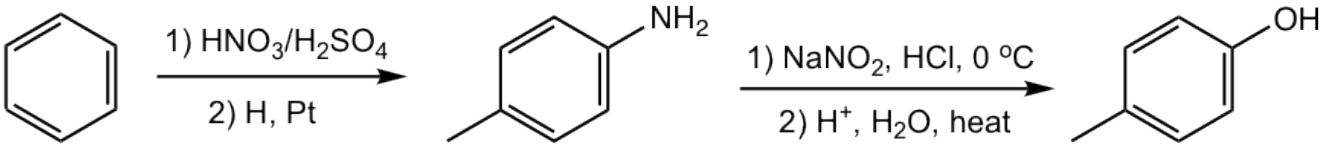


b.


Br2/FeBr3
Br
1) KMnO4, OH-
2) H3O+
HOOC
Br

major

c.


1) HNO3/H2SO4
2) H, Pt
NH2
1) NaNO2, HCl, 0 °C
2) H+, H2O, heat
OH

CHAPTER 6: REACTION AT THE A-CARBON OF CARBONYL COMPOUNDS

In Chapter 2, we saw that there are ***three*** reactivity centers of the carbonyl compounds. While the discussions in Chapter 2 focus on the reaction of the carbonyl group, in this chapter we will explore the acidity of hydrogen atoms on the carbon atom adjacent to the carbonyl group in aldehydes and ketones. The carbon adjacent to the carbonyl group is called **α-carbon**, and the hydrogen atoms on α-carbon are called the **α-hydrogens.**

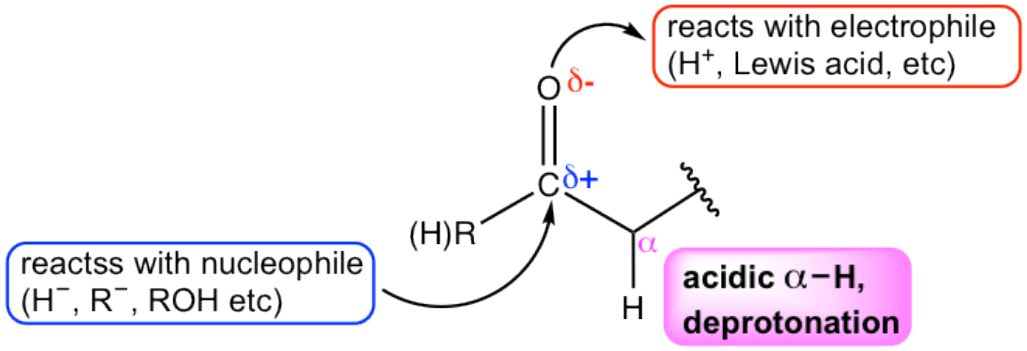


Fig. 6a Reactivity centers of carbonyl compounds (aldehydes and ketones)

6.1 The Acidity of the α-Hydrogens

Generally, the hydrogen atoms attached to sp^3 carbons, for example in alkanes, are rather weak acids with pKa over 50. However, the ***α*-hydrogens** in the carbonyl compound, which also bond to the sp^3 carbon, are much more acidic with pK_a in the range of 16 to 20 (refer to **section 3.3 in Book I** for more discussions about pKa of different functional groups).

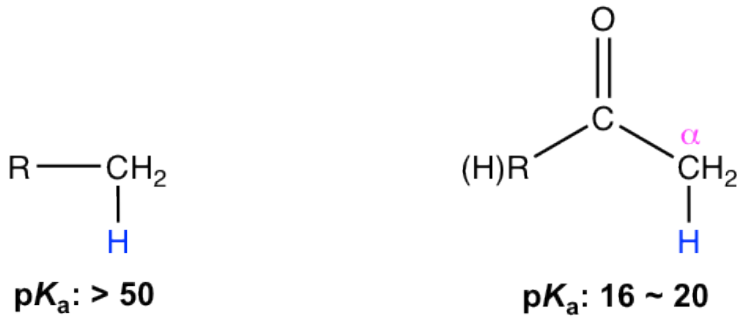


Fig. 6.1a Acidity difference of α-hydrogen in carbonyl compounds vs alkanes

The presence of the carbonyl group is the reason behind the unusual acidity of the α hydrogens. For the anion that is produced after the loss of α hydrogen, the negative charge is delocalized to the carbonyl group via resonance effect, therefore the anion is stabilized significantly. The anion (or the conjugate base on the carbonyl compound) is called **enolate**. Both resonance structures **A** and **B** can be written for the structure of enolate, and the structure **B** makes more contributions to the hybrid because the negative charge is on oxygen, the atom with higher electronegativity.

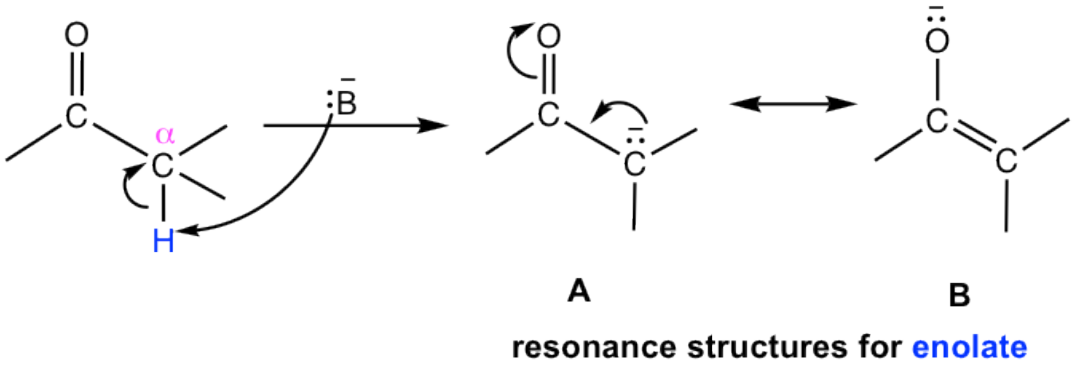


Fig. 6.1b Generation of the enolate and two resonance structures

Keto and Enol Tautomers

When enolate accepts a proton, the protonation could occur on either carbon or oxygen and gives the two forms of the carbonyl compound, **keto form** and **enol form** respectively. The term "**enol**" means alk**en**e + alcoh**ol**. The two forms are called **tautomers,** a special type of constitutional isomer (refer to **section 10.8.3 in Book I**). Keto and enol tautomers differ in the location of the double bond and hydrogen.

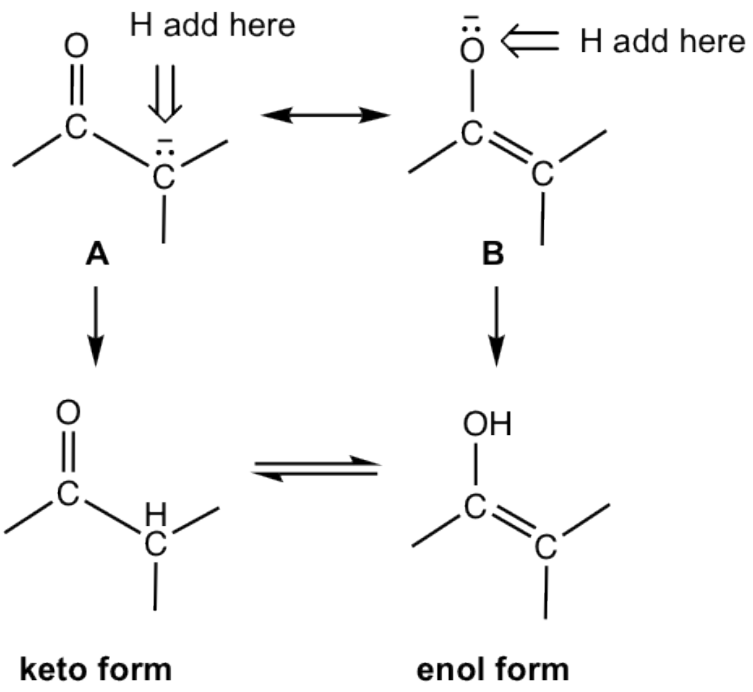


Fig. 6.1c Keto form and enol form of aldehydes and ketones

Tautomers are isomers that are in rapid equilibrium, and the interconversion between different tautomers is called tautomerization. For most aldehydes and ketones, the keto form is much more stable than the enol tautomer, and is predominant in the equilibrium.

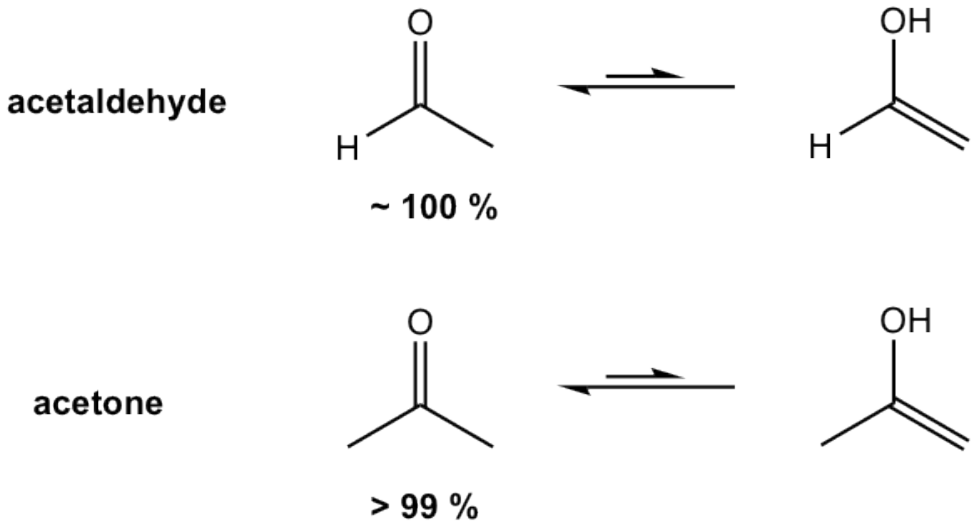


Fig. 6.1d Equilibrium between keto form and enol form

An example of the special case in which enol form is the major species applies to β-diketones (more discussions in **section 6.5**). The amount of enol present at equilibrium is much higher than keto because enol is stabilized by two effects: the intramolecular hydrogen bonding and the conjugated double bonds.

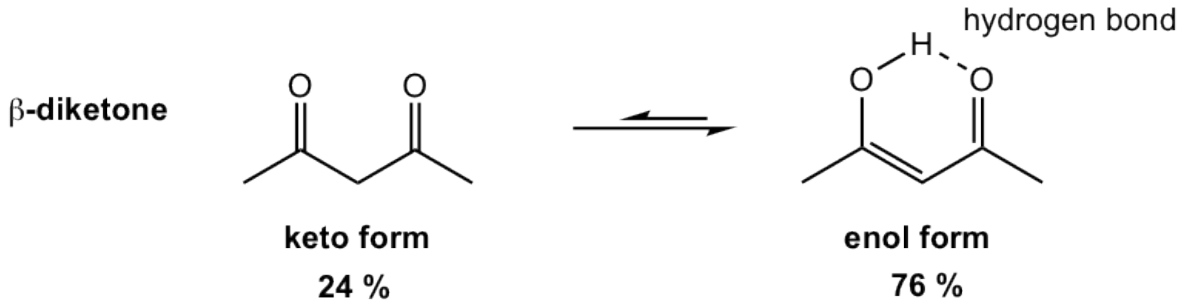


Fig. 6.1e Equilibrium between keto form and enol form for b-diketones

Keto and Enol Tautomerization

The tautomerization between keto and enol can be catalyzed by either an acid or a base, with the mechanism shown below.

In acidic conditions (Fig. 6.1f), the process is initiated by the protonation of the double bond, then followed by deprotonation of the α hydrogen.

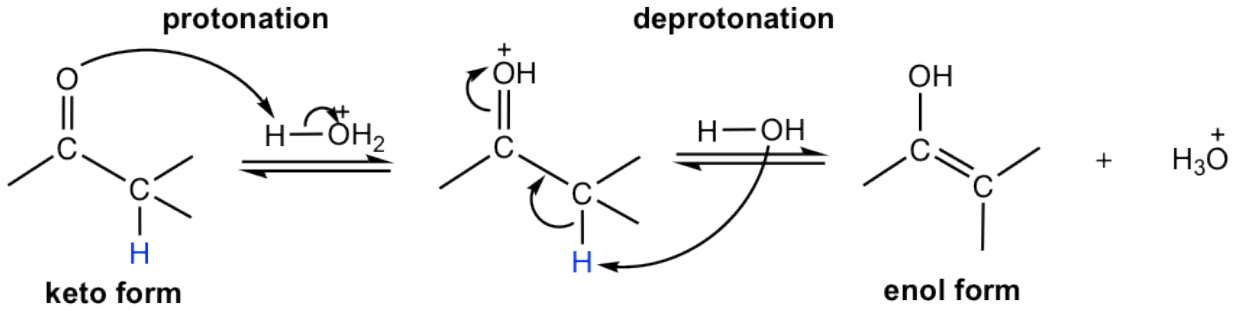


Fig. 6.1f Tautomerization between keto and enol form under acidic condition

Under basic conditions (Fig. 6.1g), the mechanism goes with the opposite order in which the α hydrogen is deprotonated first, then protonation of the enolate gives the enol form compound.

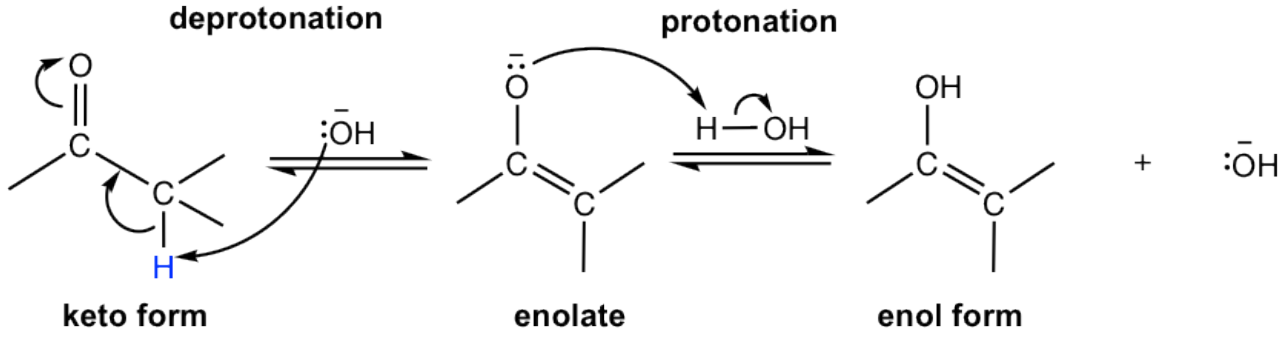
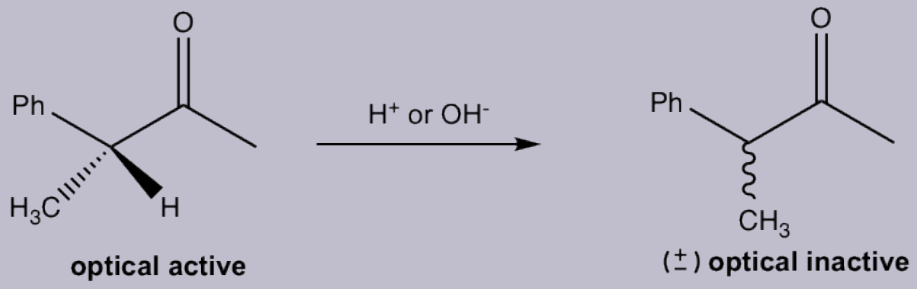


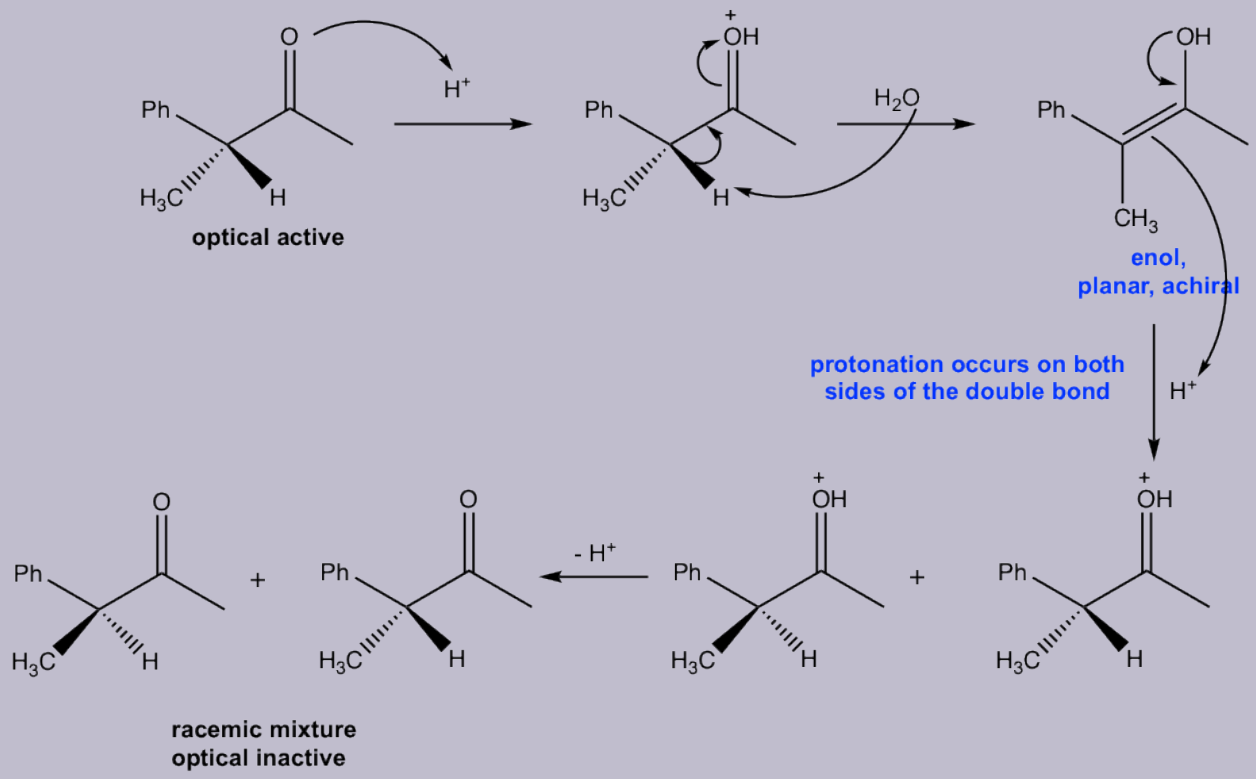
Fig. 6.1g Tautomerization between keto and enol form under basic condition

Examples

When a solution of the following chiral sample is treated with acid (or base), the solution gradually loses its optical activity. Explain the reason for this observation and show the reaction mechanism.



Answers: The mechanism for the reaction in acidic conditions is shown here for explanation.



In the presence of acid, the keto form undergoes tautomerization to become the enol form, which is planar and achiral. When enol converts back to keto, the protonation of the double bond could take place ***on either***

side of the plane, therefore producing equal amounts of both enantiomers for the keto form, that is the racemic mixture. So the solution becomes optical inactive.

6.2 Halogenation of the α-Carbon

When halogen (Cl_2, Br_2, or I_2) is added to the aldehyde or ketone, one or more of the α-hydrogens are replaced by halogens. The reaction proceeds with either acid or base present, through different reaction mechanisms.

Acid-Catalyzed Halogenation

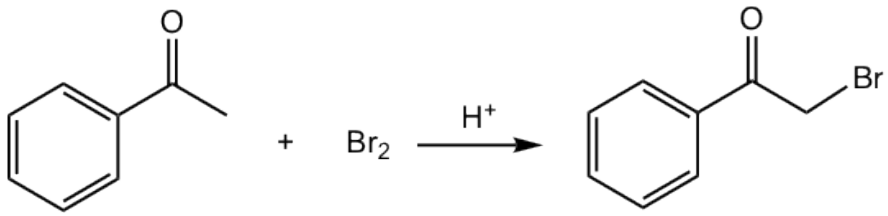


Fig. 6.2a Acid-catalyzed bromination of acetophenone

In acid-catalyzed halogenation, only **one** α-hydrogen is replaced by a halogen. The reaction mechanism (Fig. 6.2b) involves the formation of enol in acidic conditions in the first step, then the addition of halogen with enol followed by deprotonation.

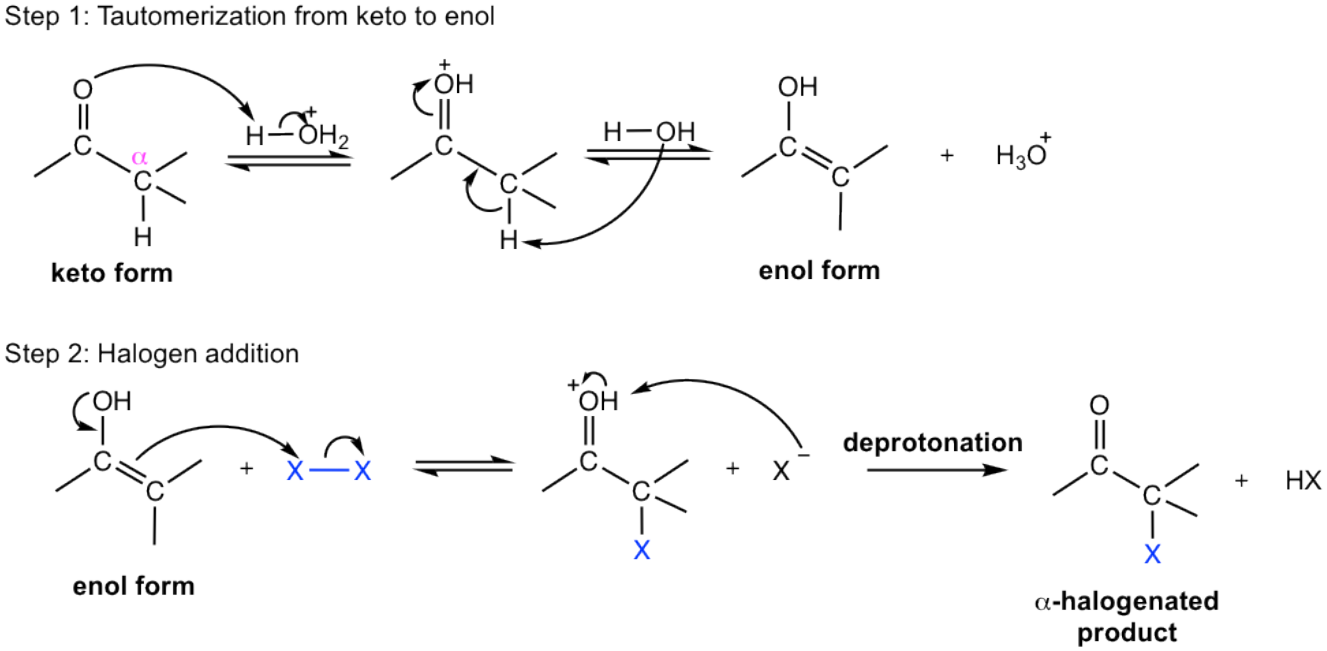


Fig. 6.2b The mechanism for acid-catalyzed α-halogenation of aldehyde or ketone

For α-halogenated aldehyde/ketone, because of the inductive electron-withdrawing effect of halogen, the electron density of the C=O group is lower than that in a regular aldehyde/ketone, so further protonation is not favored. Since protonation is the very first step in the mechanism, no further halogenation occurs. That explains why halogenation only takes place only once in acidic conditions.

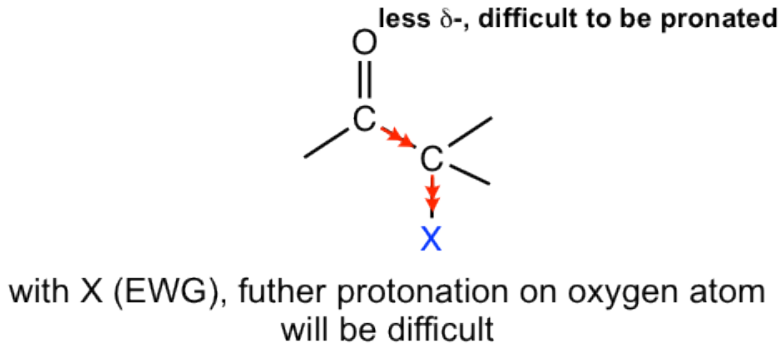


Fig. 6.2c α-halogenated aldehyde/ketone cannot be protonated

Base-Promoted Halogenation

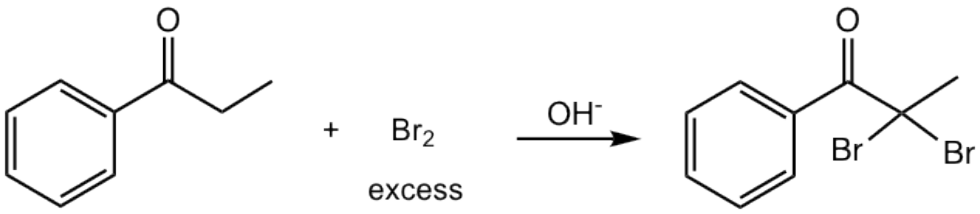


Fig. 6.2d Base-promoted bromination of ethylphenylketone

Under basic conditions, ***all*** of the α-hydrogens are replaced by excess halogens, with the halogenation process repeated multiple times.

This can be explained by the mechanism shown in Fig. 6.2e. The first step of halogenation is the deprotonation of the α-hydrogen, so enolate is generated. The enolate then reacts with halogen to produce the α-halogenated product. With the first halogen introduced in the structure, the inductive electron-withdrawing effect of halogen increases the acidity of the remaining α hydrogens, so the successive halogenations are more rapid and repeated more easily.

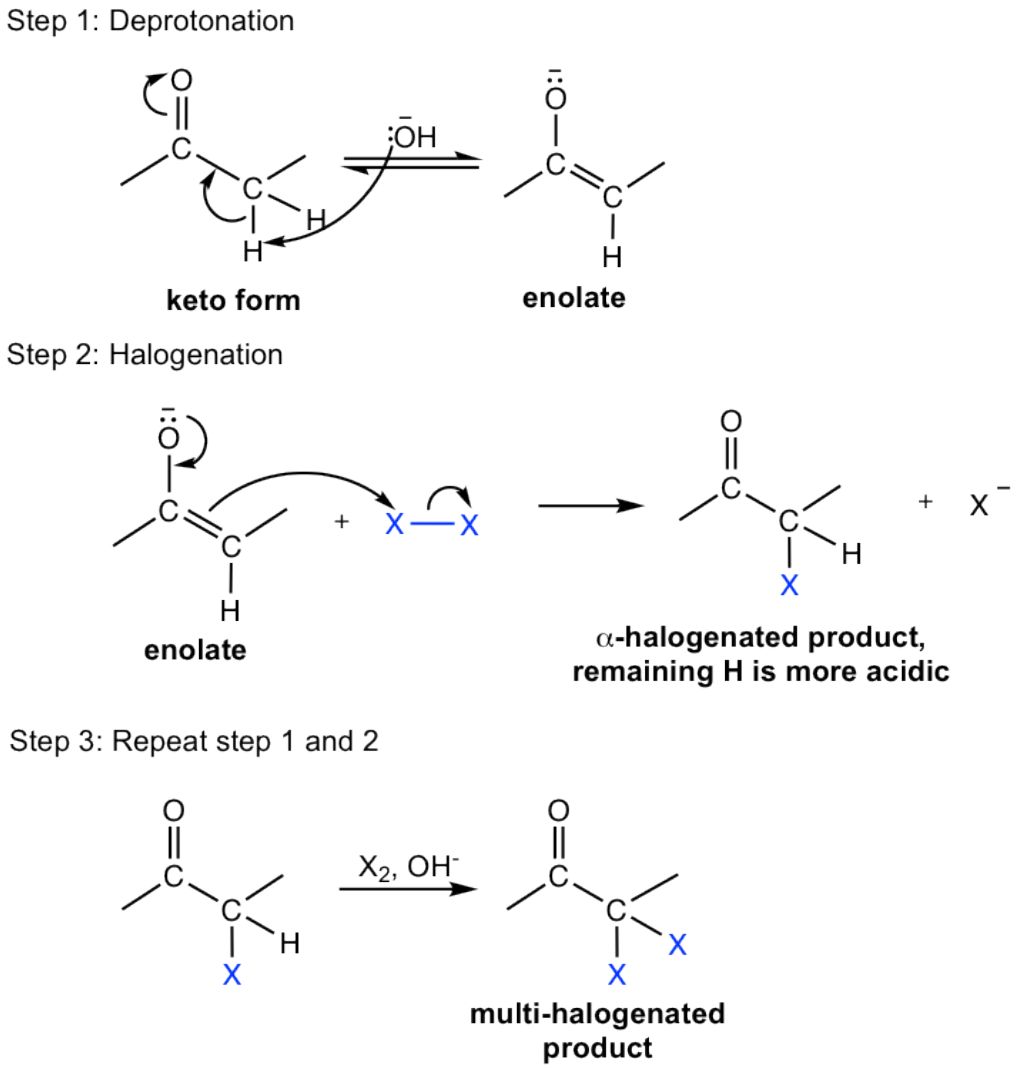


Fig. 6.2e Mechanism for base-promoted α-halogenation

The Haloform Reaction

When the methyl ketone reacts with excess base and halogens, the carboxylate is produced as the final organic product. The side product of such a reaction is an inorganic compound called haloform, with the formula of CHX_3, and as a result, the reaction is called a haloform reaction. When iodine is used, the bright yellow precipitate iodoform CHI_3(s) is obtained. Iodoform reaction is usually used as a test for the presence of methyl ketone.

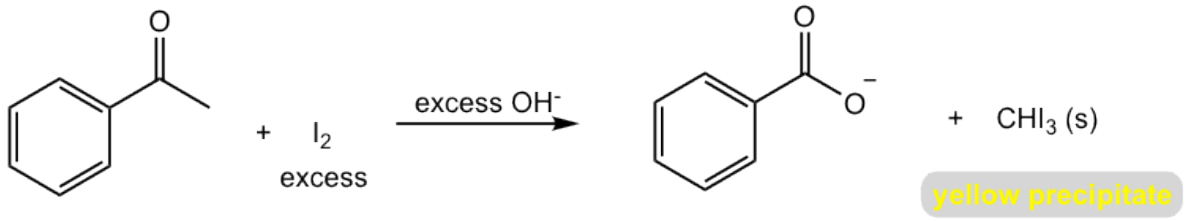


Fig. 6.2f Iodoform reaction of acetophenone

Other than being used for test purposes, the haloform reaction is also synthetically useful to prepare carboxylic acids from methyl ketones. The mechanism of haloform reaction is shown in Fig. 6.2g.

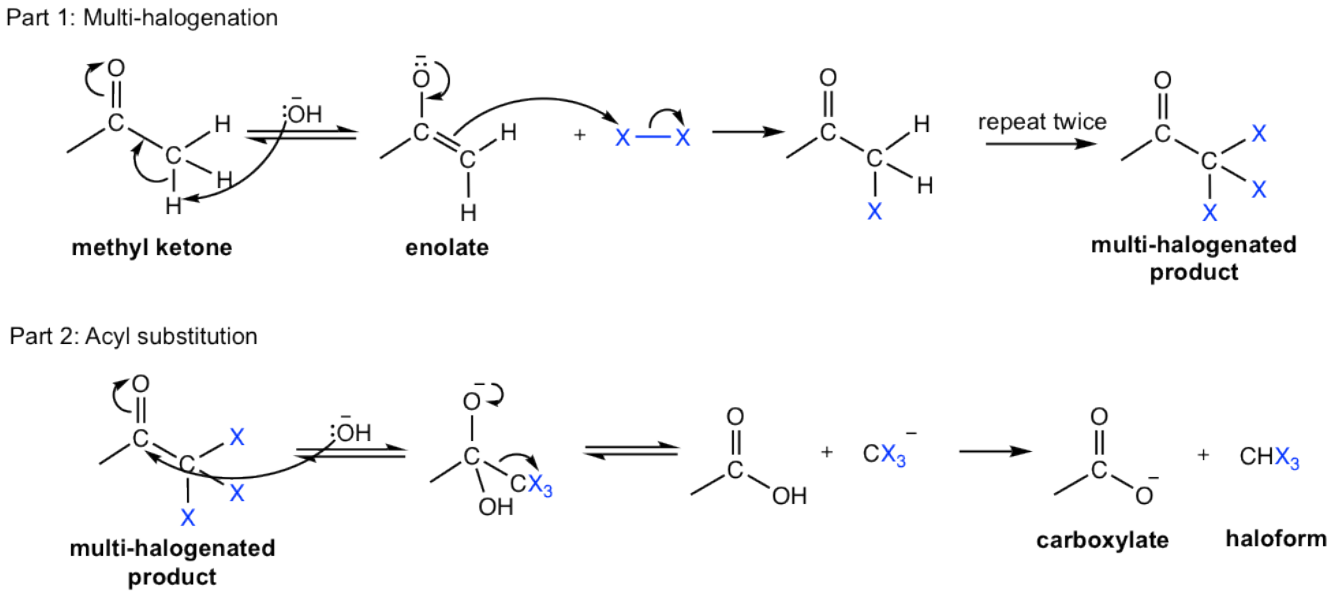


Fig. 6.2g Mechanism for haloform reaction

The first half of the haloform reaction is the same as halogenation under basic conditions, with all three α-hydrogens replaced by halogens. The resulting CX_3 group bonded to the carbonyl can be a good leaving group and then replaced by OH^- in the second half of the reaction, which leads to the formation of carboxylate salt and haloform.

6.3 Alkylation at the α-Carbon

In this section, we will have further discussions about how to generate enolate anion and the reactions of enolate.

Preparation of Enolate Ion

In earlier sections, we did see that a common base like OH^- could remove α-hydrogen. However, the amount of enolate ion generated by using OH^- is rather small, because OH^- is a weaker base than the enolate and the reaction equilibrium mainly lies on the reactant side (refer to acid-base reaction equilibrium in **section 3.3 in Book I**).

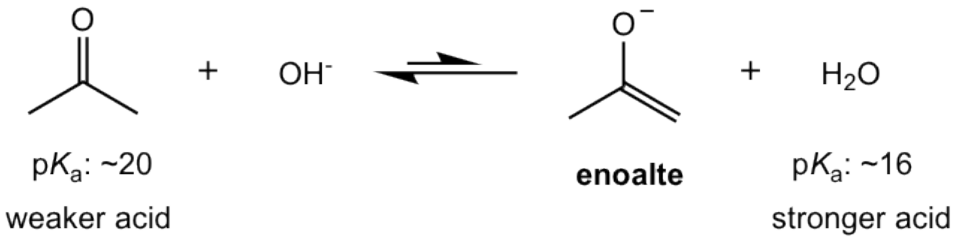


Fig. 6.3a Generation of enolate with OH- (the enolate is shown with only one resonance structure)

To produce enolate in good yield, a stronger base is therefore required. The most common base employed for this purpose is lithium diisopropylamide (LDA). As the conjugate base of a much weaker acid diisopropylamine (with pKa of about 35), LDA is a much stronger base than enolate and the equilibrium lies on the product (enolate) side predominantly. LDA is the choice of base for the reactions that require carbonyl compound to be completely converted to enolates before further reactions.

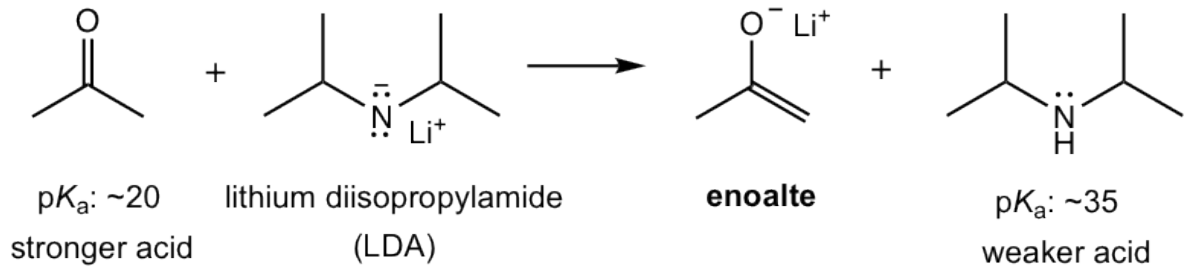


Fig. 6.3b Preparation of enolate with LDA as base

LDA is a strong bulky base that can be prepared by adding alkyllithium to diisopropylamine in a polar aprotic solvent such as THF at the low temperature of -78 °C. Low temperature is usually required to prepare and handle LDA because of the high reactivity.

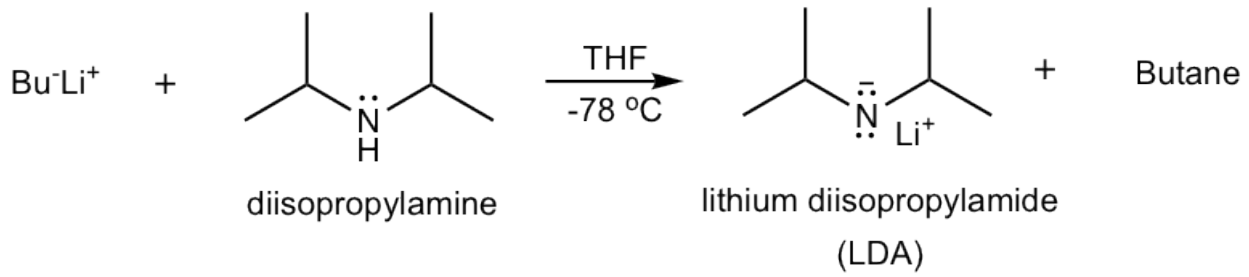


Fig. 6.3c Preparation of LDA

For asymmetric ketone that has α–hydrogens on different α–carbons, such as 2-methylcyclohexanone, the enolate could be generated on either side depending on the reaction condition employed (Fig. 6.3d).

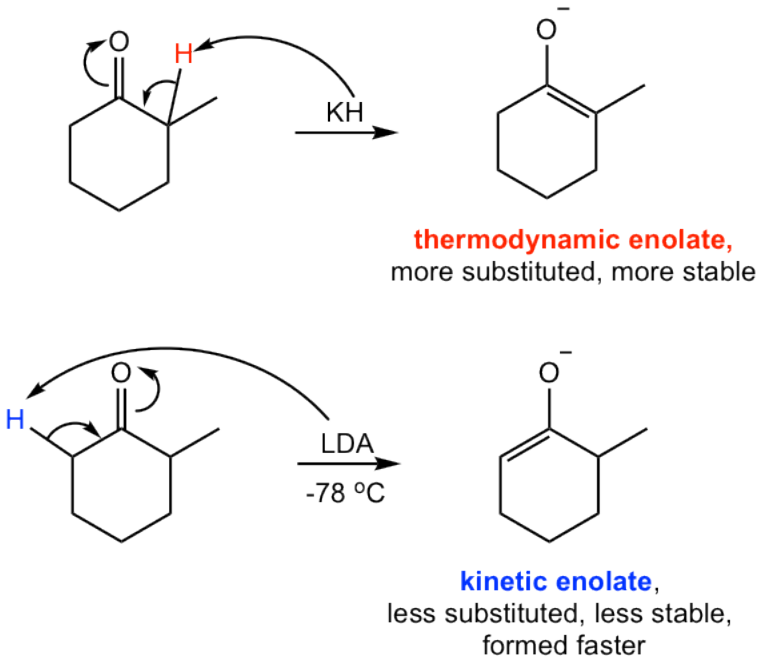


Fig. 6.3d Thermodynamic enolate and kinetic enolate

The enolate ion formed by the removal of the α-hydrogen (red one) on the more sterically hindered side is highly substituted and, therefore is thermodynamically more stable, so is called the **thermodynamic enolate**. The other one formed by the removal of the α–hydrogen (blue one) on the less sterically hindered side is less substituted, not as stable, but is formed faster because of less steric hindrance, such enolate is called the **kinetic enolate**. The use of a strong bulky base, such as LDA, at low temperature favors the formation of a **kinetic enolate**, and the use of a small size base, such as KH, at higher temperature favors the formation of a **thermodynamic enolate**.

Direct Alkylation via Enolate

The enolate ion, with a negative charge, is nucleophilic and reacts with electrophiles. When enolate reacts with an alkyl halide, the reaction proceeds in a similar way as the S_N2 reaction, and an alkyl substituent is introduced onto the α carbon. In the following example, the ethyl group is introduced onto a carbon of cyclohexanone by a two-step process.

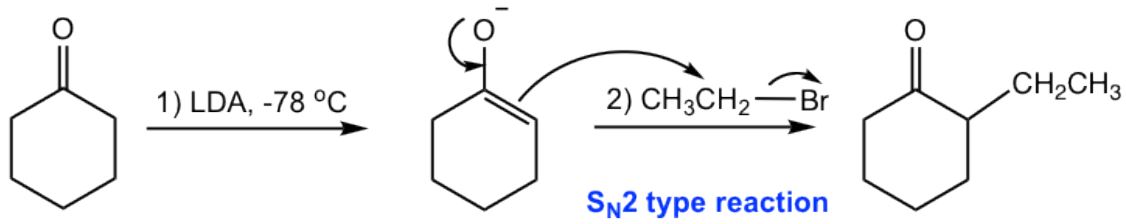


Fig. 6.3e Direct alkylation of enolate

This is an important and useful reaction in organic synthesis because it provides another way to form carbon-carbon bond, and build larger molecules. Because it is an S_N2-type reaction, it works best with methyl and primary alkyl halides.

Indirect Alkylation via Enamine

An alternative way of alkylation is via the enamine derivative of aldehyde and ketone. Recall that enamines are produced when aldehydes or ketones react with secondary amine (**section 2.7.3**), and enamine is also a good nucleophile and can react with alkyl halides in S_N2-type reactions to produce iminium ion. The hydrolysis of the iminium ion intermediate gives the alkylation product. This method offers another way to add an alkyl group to the α-carbon of a carbonyl compound.

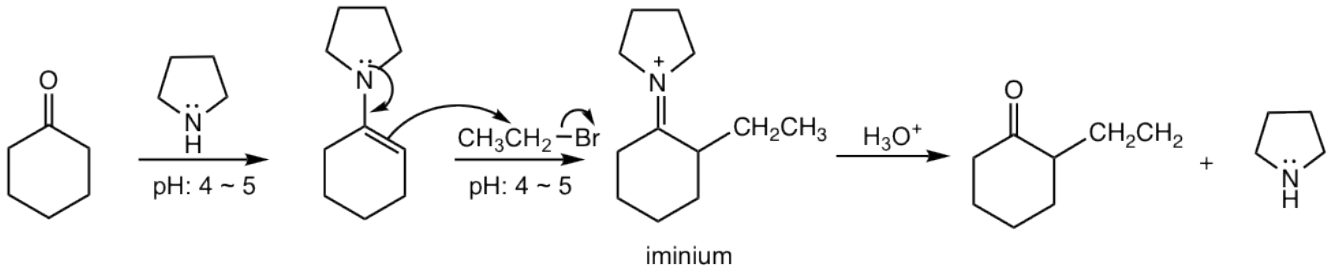


Fig. 6.3f Alkylation of ketone via enamine

6.4 Aldol Reactions

6.4.1 Aldo additions and aldol condensations

Another very important type of reaction to build a carbon-carbon bond by applying enolate is the **aldol reaction**, which includes **aldol additions** and **aldol condensations**.

Aldol reaction is the reaction between enolate (or enol), which acts as a nucleophile, and the electrophilic carbonyl group of the other aldehyde or ketone molecule. Since enolate also comes from the deprotonation of aldehyde or ketone, the aldol reaction is the reaction between two molecules of carbonyl compounds, as shown below in Fig. 6.4a.

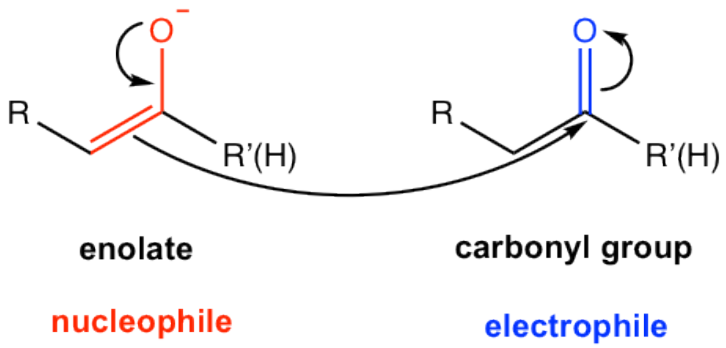


Fig. 6.4a Aldol reaction: reaction between enolate and carbonyl group

Aldol addition is the reaction in which the two carbonyl compounds are added together, and produce **β-hydroxy aldehyde or ketone** as a product. The name "**aldol**" comes from b-hydroxy aldehyde because it contains both an **ald**ehyde and an alcoh**ol** functional group.

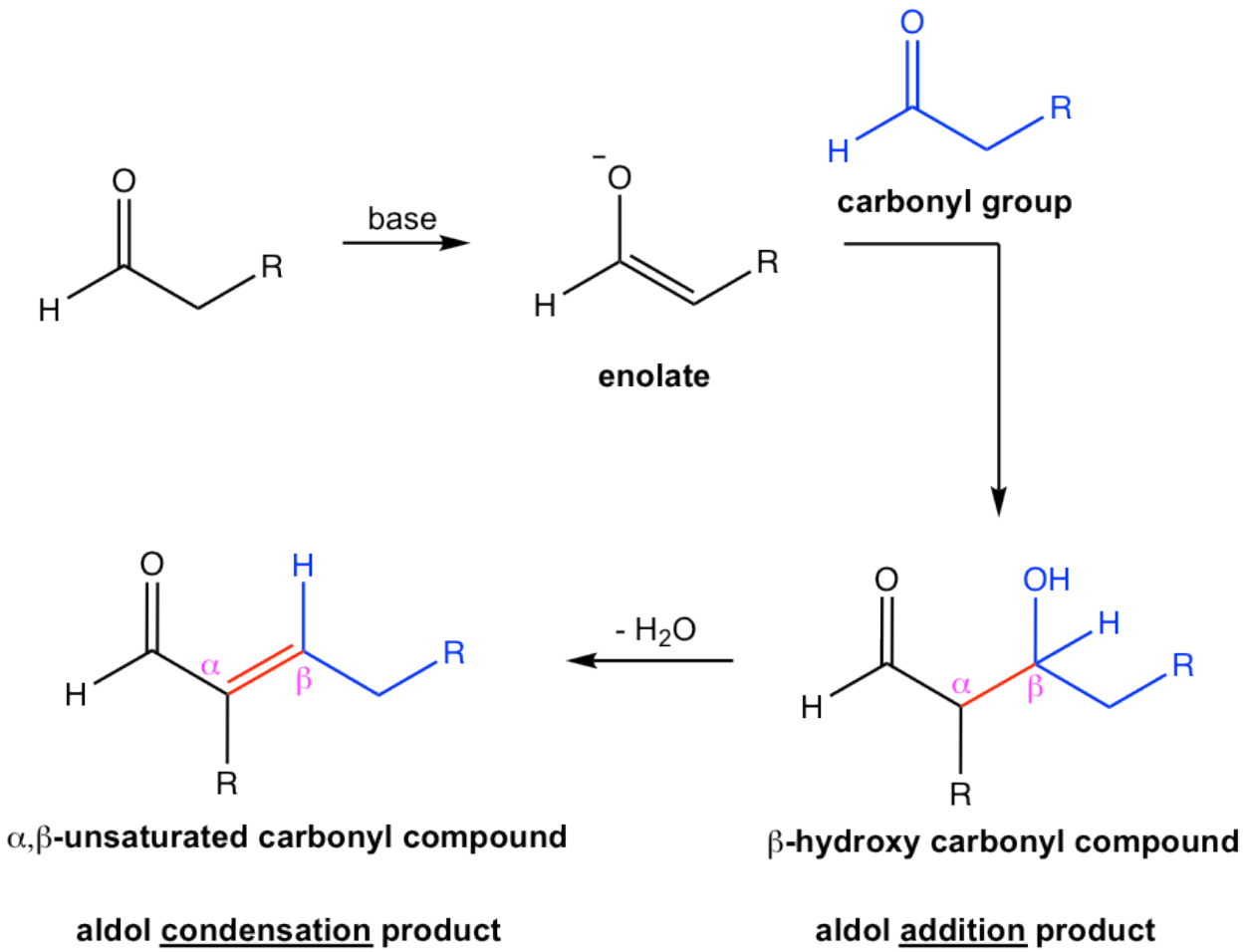


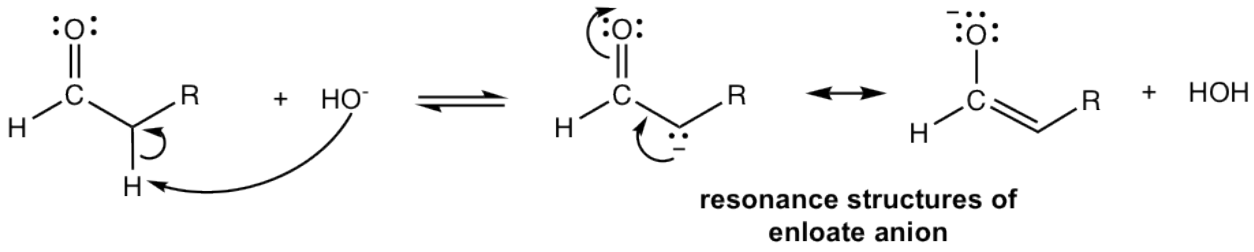
Fig. 6.4b General reaction equation for aldol addition and aldol condensation

The initial aldol addition product could also undergo a dehydration reaction, and give α,β-unsaturated aldehyde/ketone, and then the overall reaction is an **aldol condensation.**

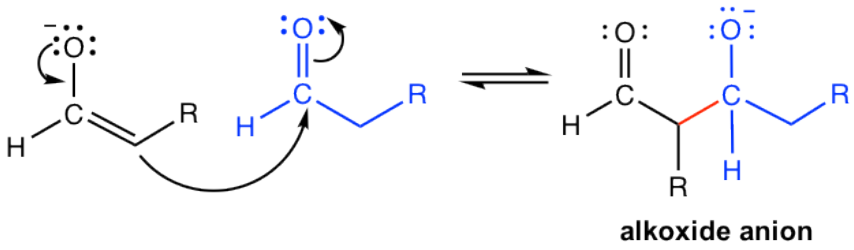
We will take closer a look at the reaction mechanism for aldol reactions.

Aldol Additions

Step 1: Generation of enolate



Step 2: Nucleophilic addition of enolate to carbonyl group



Step 3: Protonation of the alkoxide

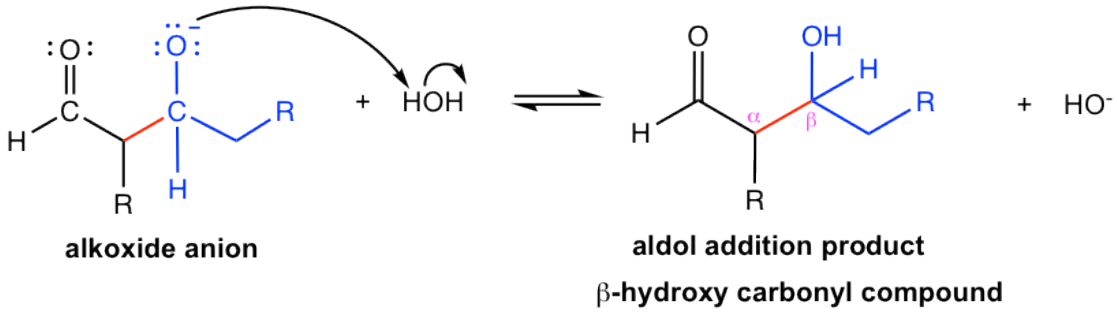
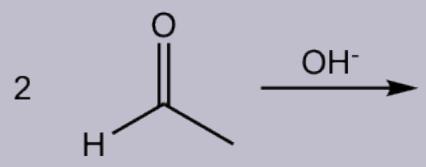


Fig. 6.4c The mechanism for aldol addition

With hydroxide (OH^-) or alkoxide (OR^-) commonly used as bases, aldol addition is a reversible reaction that stays at equilibrium. The decent yield of aldol addition product could be obtained for aldehydes, because of the higher reactivity of carbonyl group in aldehyde. Ketones are less susceptible to aldol addition due to lower reactivity. However, as we will see in the next section dehydration of the aldol addition product helps the equilibrium to move towards completion, for both aldehydes and ketones.

Examples

Show the aldol addition product of the following reaction.



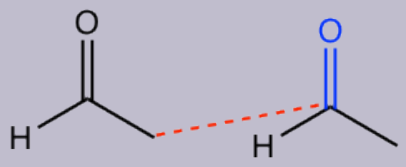
acetaldehyde

Tips on how to figure out the aldol addition product:

An important/useful hint is that the addition product is like an "adduct", with a new C-C bond formed between the α-carbon of one molecule and the carbonyl carbon of the other molecule, and the carbonyl group turns into an OH group. The total number of carbons in the product is the **sum** of the number of carbons in each molecule.

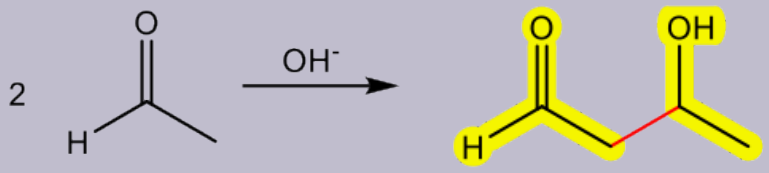
Strategy:

- Apply the hint mentioned above to connect the two molecules, as shown by the red dotted line below.



- Change the blue carbonyl to the OH group, and redraw the structure of the product in a reasonable way.
- Double-check the answer: Does the total number of carbons match? Is it a β-hydroxy aldehyde?
- – Yes, the product is a β-hydroxy aldehyde with a total of 4 carbons.

Answer:



acetaldehyde **3-hydroxybutanal**

Aldol Condensations

When the aldol addition product undergoes dehydration, an α,β-unsaturated aldehyde or ketone is formed and the overall reaction is called an aldol condensation. Because α,β-unsaturated aldehyde or ketone is a **conjugated system**

with the C=C double bond conjugated with the carbonyl group, it shows special stability, and therefore dehydration occurs easily upon heating.

For example of the aldol addition product 3-hydroxybutanol in the previous example, dehydration under the basic condition leads to the formation of aldol condensation product 2-butenal (Fig. 6.4d). With low temperature, aldol addition product is obtained; and aldol condensation product is obtained with heating.

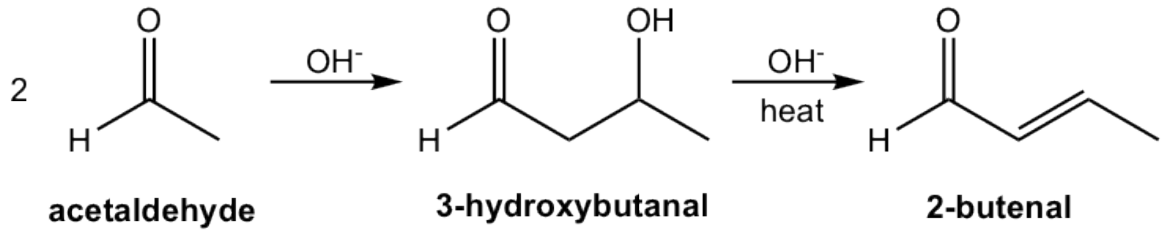


Fig. 6.4d Aldol addition and condensation reaction of acetaldehyde

In the mechanism for dehydration (Fig. 6.4e), the α-hydrogen is deprotonated first, then the OH group leaves. The dehydration step is irreversible. The special stability of the conjugated system with alkene and carbonyl group is the driving force that leads to the completion of the reaction.

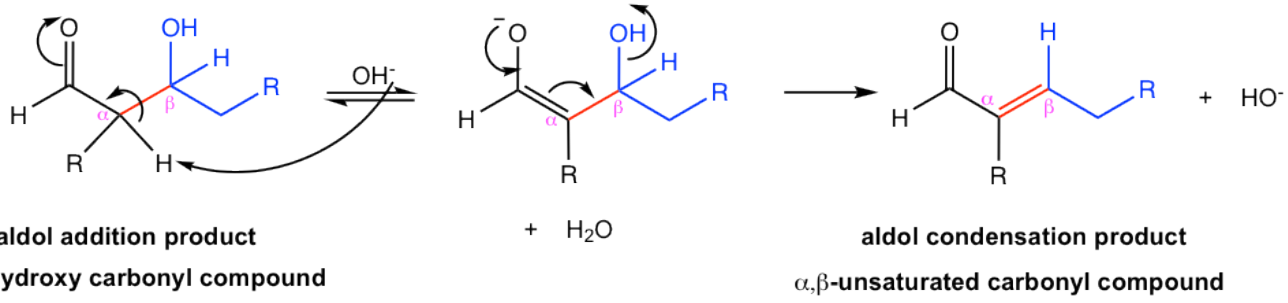
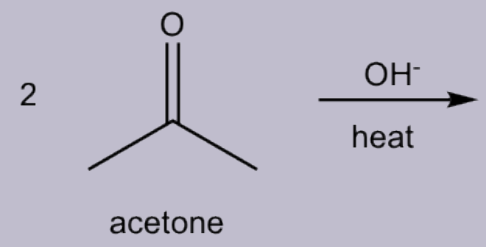
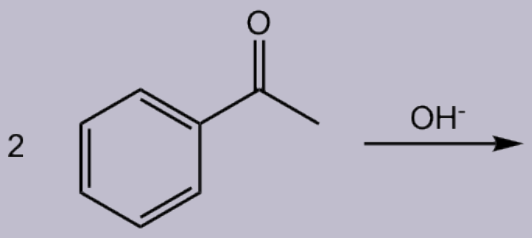


Fig. 6.4e Mechanism for Dehydration

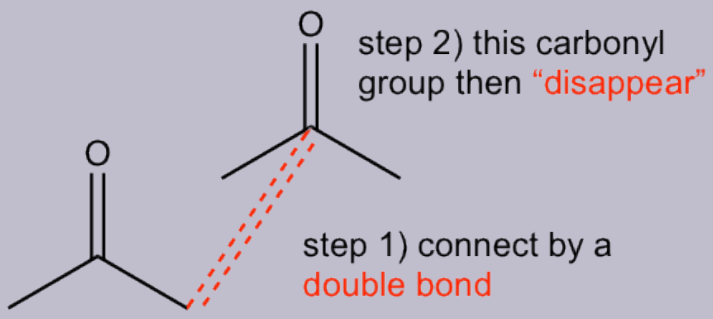
Examples

Show aldol condensation product:

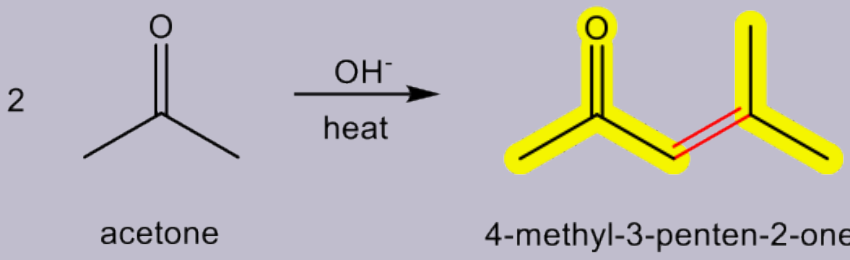


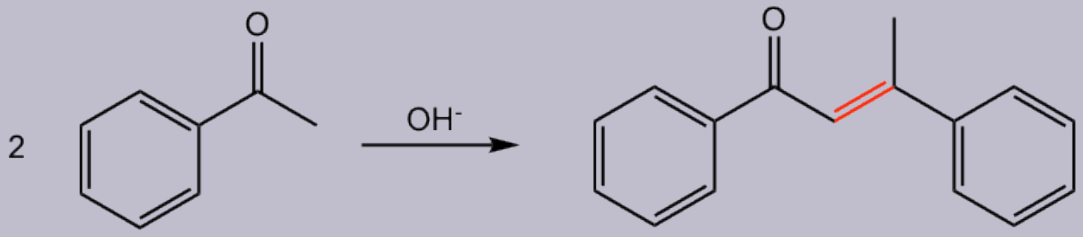


Strategy: (Take the first reaction as an example)



Answer:





In the 2nd reaction here, a large extended conjugated system with two benzene rings is built with the formation of the new double bond. The special stability of the conjugated system makes the dehydration of this reaction occur easily and heating is not even necessary.

6.4.2 Cross Aldol Reaction

When two different carbonyl compounds, for example, A and B, are mixed together in an aldol reaction, four products could be formed statistically if no specific conditions are controlled. We will take the example of aldol condensation between acetaldehyde (**A**) and propanal (**B**) as an example. Both compounds can donate either enolate or the carbonyl group, so four possible products in total come from the combinations A-A, B-B, A-B, and B-A. The reactions from the combination of A-B or B-A are called cross aldol reactions.

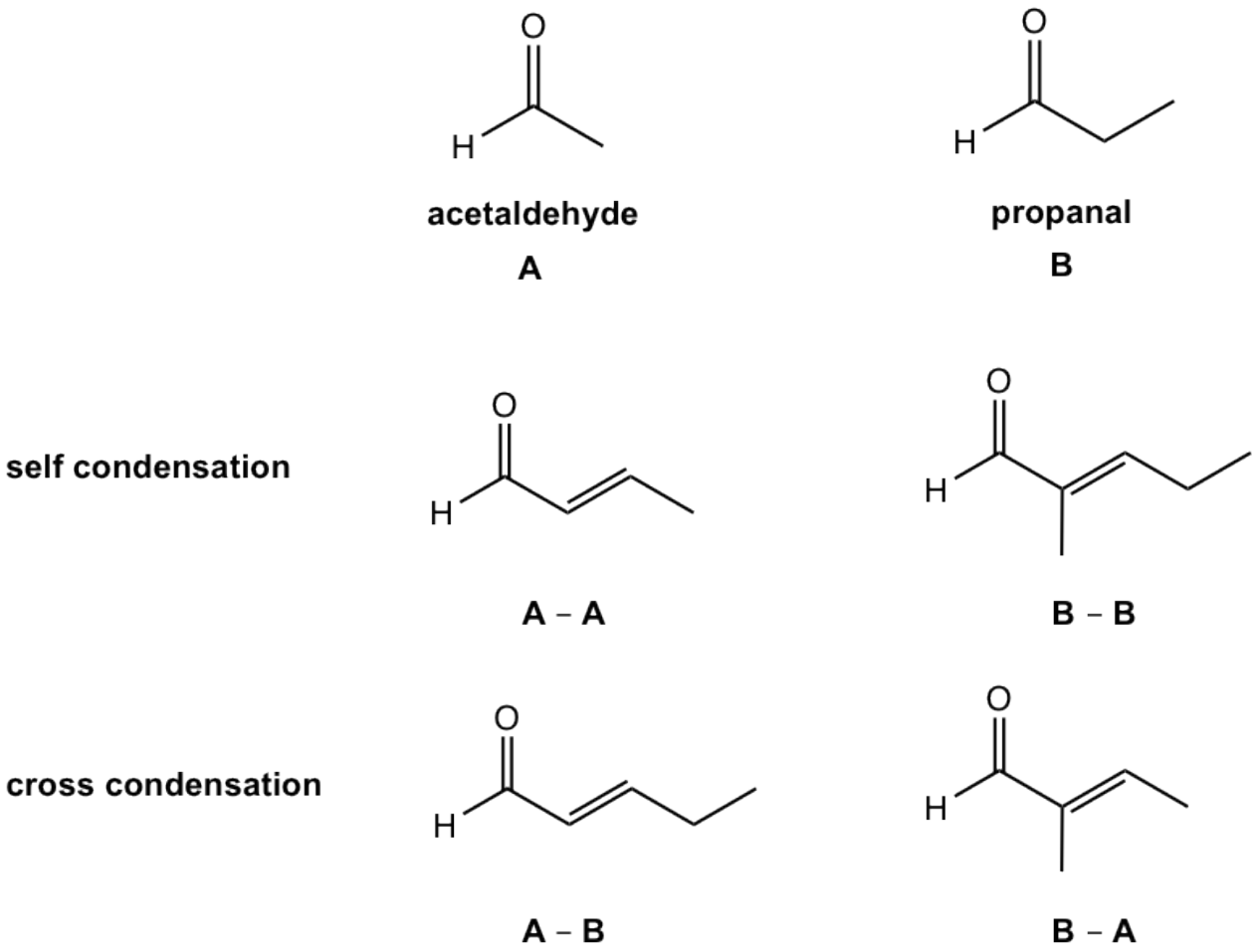


Fig. 6.4f Aldol condensation products when mixing acetaldehyde (**A**) *and propanal* (**B**)

It is usually difficult to separate the four products apart since they have similar structures and similar physical properties, so the aldol reaction that produces four products is not useful for synthesis purposes.

On the other hand, if the structures of carbonyl compounds and reaction conditions are carefully controlled, a cross aldol reaction could only produce one single product, it therefore could be used as a synthetic tool.

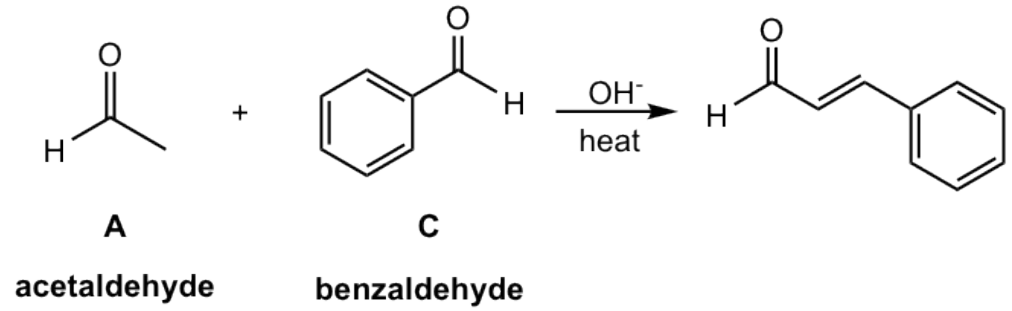


*Fig. 6.4g Crosse aldol condensation between acetaldehyde (**A**) and benzaldehyde (**C**)*

In the above reaction in Fig. 6.4g, only compound **A** (acetaldehyde) has an α-hydrogen, while compound **C** (benzaldehyde) does ***not*** have an α-hydrogen. Since **C** has no α-hydrogens, it cannot do self-condensation. The reaction is also carried out in a way that compound **A** is added slowly to a solution of compound **C** with base OH^-. Since the concentration of compound **A** is always low under this condition, and it is present mostly in its enolate form, the possibility of self-condensation of compound **A** is also minimized. Therefore the reaction could only take place between the enolate of compound **A** and the carbonyl group of compound **C**, and produce the single product.

A couple of other carbonyl compounds with no α-hydrogen that are used commonly in crossed aldol reactions are listed in Fig. 6.4h.

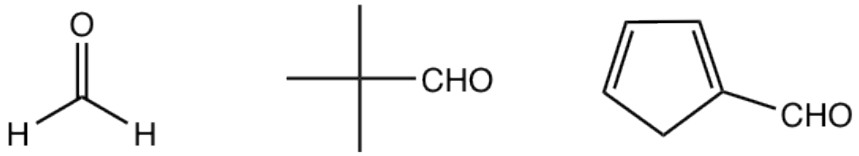


Fig. 6.4h Carbonyl compounds with no α-hydrogen

6.4.3 Intramolecular Aldol Condensation

For a molecule that contains two carbonyl functional groups in the proper positions, the aldol condensation could take place intramolecularly to produce a cyclic product with **five-** or **six-membered** rings, and the reaction is also called aldol cyclization.

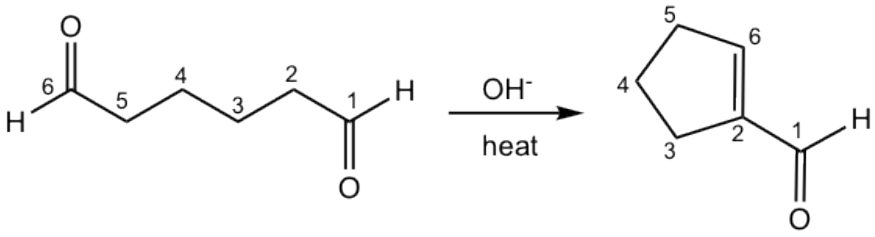


Fig. 6.4i Intramolecular aldol condensation example

For the above reaction, one aldehyde provides enolate and the aldehyde on the other end provides the carbonyl group (as shown in the hint drawing). This example also represents a symmetric dialdehyde that only one product is possible for aldol cyclization.

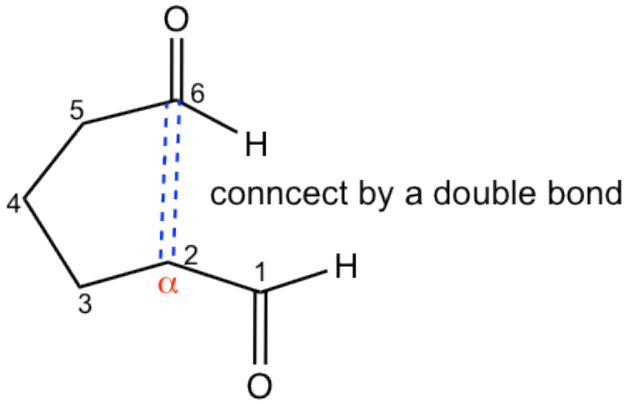
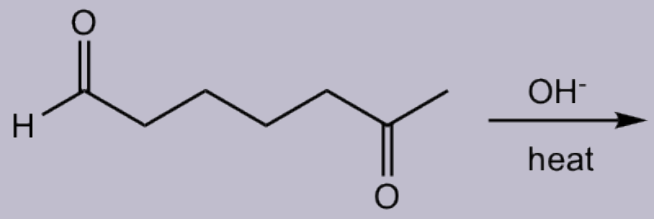


Fig. 6.6j Hint for drawing the product of reaction in Fig. 6.4i

Let's take a look at another example for the reaction of a keto aldehyde, and see how to decide the major product if multiple reaction pathways are available.

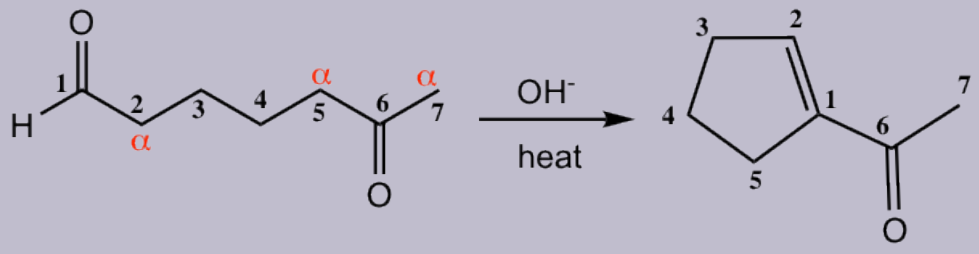
Examples

Show the product.



Analysis and answer:

Three different enolates are possible because there are two types of α-hydrogens on each side of ketone, and one type α-hydrogen of the aldehyde. However, the major product formed is the five-membered ring and this could be explained for two reasons:



- The carbonyl group in aldehyde shows a higher reactivity than that in ketone towards nucleophilic reaction, so the reaction takes place preferentially on the aldehyde carbonyl group.
- Five-membered rings form far more feasibly than seven-membered rings because of their stability, so the reaction occurs between the enolate from C-5 and the carbonyl group on C-1.

6.5 Reactions of α,β-unsaturated Aldehydes and Ketones

α,β-unsaturated aldehydes and ketones are the products of aldol condensations. Two functional groups, C=C bond alkene, and C=O bond carbonyl, presented in this type of compound in the ***conjugated*** way. The reactivities of α,β-unsaturated aldehydes and ketones therefore are determined by such special structure features.

As we have learned the C=O bond is ready to undergo nucleophilic addition (**section 2.3**). Similarly, the addition is also the most typical reaction for the C=O bond in α,β-unsaturated aldehydes and ketones. However, depending on the structure of the nucleophile, the nucleophilic reaction could take place in two different ways: **simple addition** in which the addition just occurs in the C=O group, or **conjugate addition** in which the C=C bond is involved in the addition as well.

Simple addition is also called **1,2-addition**, and the conjugate addition is usually named **1,4-addition**, as illustrated below in Fig. 6.5a. The numbers here (1,2 or 1,4) are for the purpose of labeling the atoms involved in the conjugated system, and have nothing to do with the numbering in the IUPAC name of the compound. The structures shown in Fig. 6.5a are general structures.

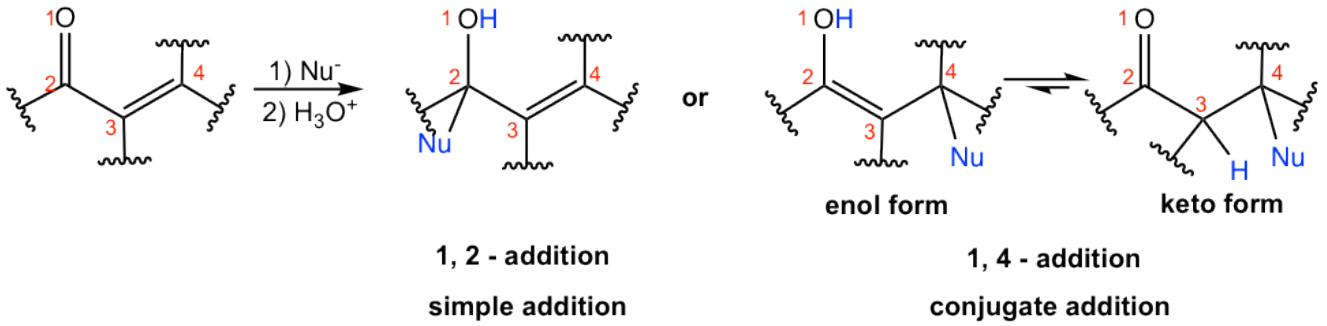


Fig. 6.5a 1,2- or 1,4-addition of α,β-unsaturated carbonyl compounds

Why the addition could be either 1,2- or 1,4-? We can get the answer by examining the resonance structures of α,β-unsaturated carbonyl compounds (Fig. 6.5b).

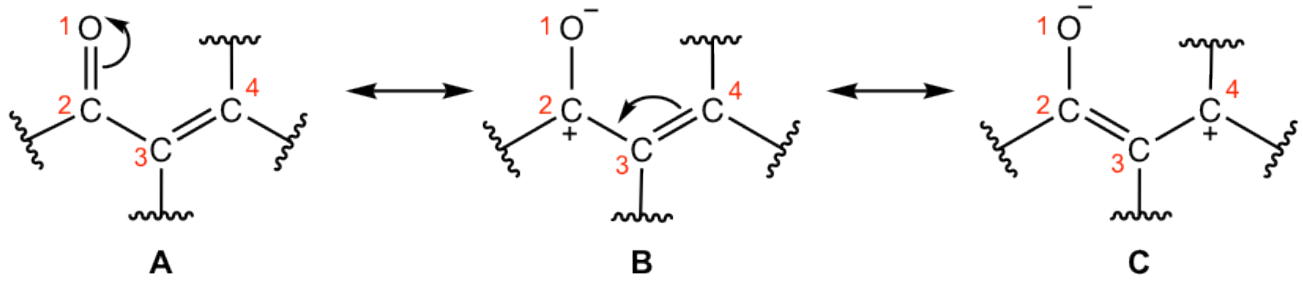


Fig. 6.5b Resonance structures of α,β-unsaturated carbonyl compounds

Both resonance structures **B** and **C** make significant contributions to the hybrid since the negative charge is on oxygen,

the atom with high electronegativity. It is indicated in structures **B** and **C** that both **carbonyl carbon** (C-2) and the **β-carbon** (C-4) bear a partial positive charge, so they both are spots where the nucleophilic attack could occur, therefore the reaction could be either 1,2- or 1,4-addition.

6.5.1 1,2-addition of α,β-unsaturated aldehydes and ketones

1,2-addition is favored when strong nucleophiles are applied to the reaction. Strong nucleophiles include the nucleophile with negative charge, for example: hydride (H^-), lithium reagent (RLi), and Grignard reagent (RMgX). The reaction mechanism is the same as simple nucleophilic addition to the carbonyl group that we learned in **section 1.4**. Another type of reagent that gives a 1,2-addition product is the **derivatives of primary amine**, which includes hydroxylamine NH_2OH, hydrazine NH_2NH_2, and semicarbazide $NH_2NHCONH_2$. The 1,2-addition products of these compounds are precipitates that serve as the driving force to make this pathway favorable (refer to **section 2.7**)

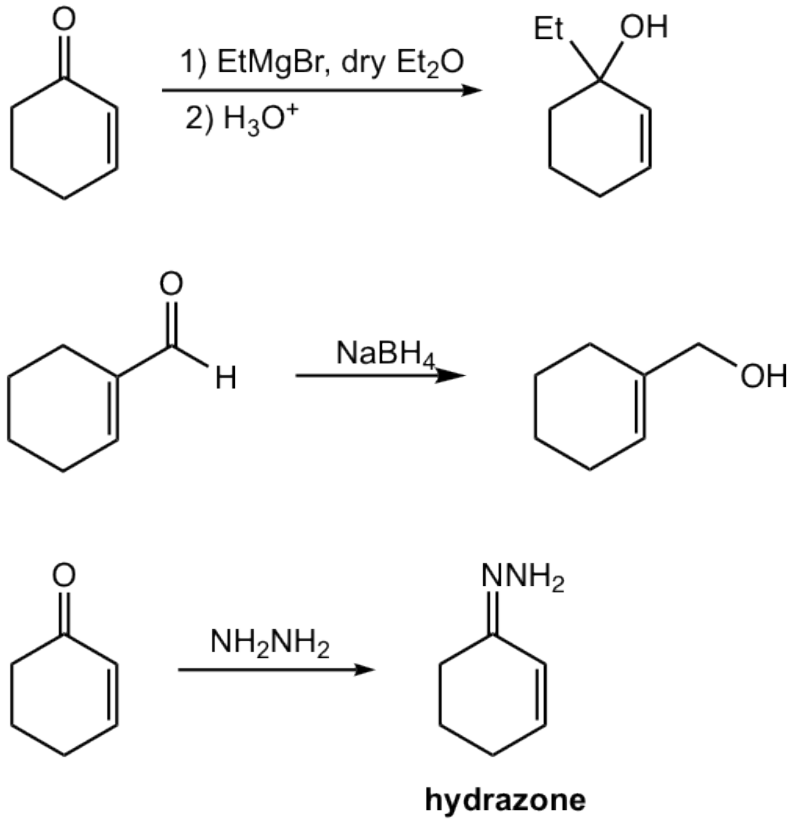


Fig. 6.5c 1,2-addition examples of α,β-unsaturated aldehydes and ketones

6.5.2 1,4-addition of α,β-unsaturated aldehydes and ketones

Generally speaking, when weaker nucleophiles are used, the 1,4-addition product is formed as the major one. The weaker

nucleophiles could be H_2O, ROH, amines, and CN^- followed by protonation. The 1,4-addition example of methyl amine to 2-cyclohexen-1-one is shown in Fig. 6.5d.

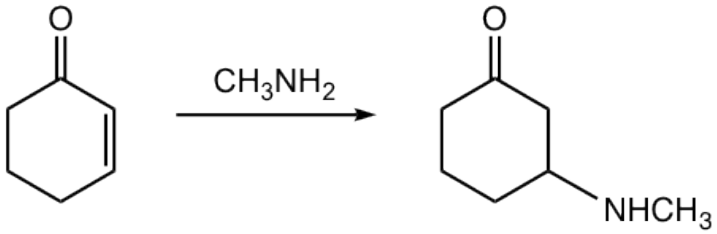


Fig. 6.5d 1,4-addition examples of α,β-unsaturated aldehydes and ketones

The mechanism for 1,4-addition of α,β-unsaturated compounds is shown in Fig. 6.5d. Nucleophile attacks at the β-carbon (C-4) first, and the enolate intermediate accepts a proton to give the enol form product. Enol form compound undergoes **tautomerization** automatically because of the higher stability of the keto form and produces keto form as the final product. ***Please note that the final product seems to arise from 3,4-addition, but it is actually through the 1,4-addition mechanism!***

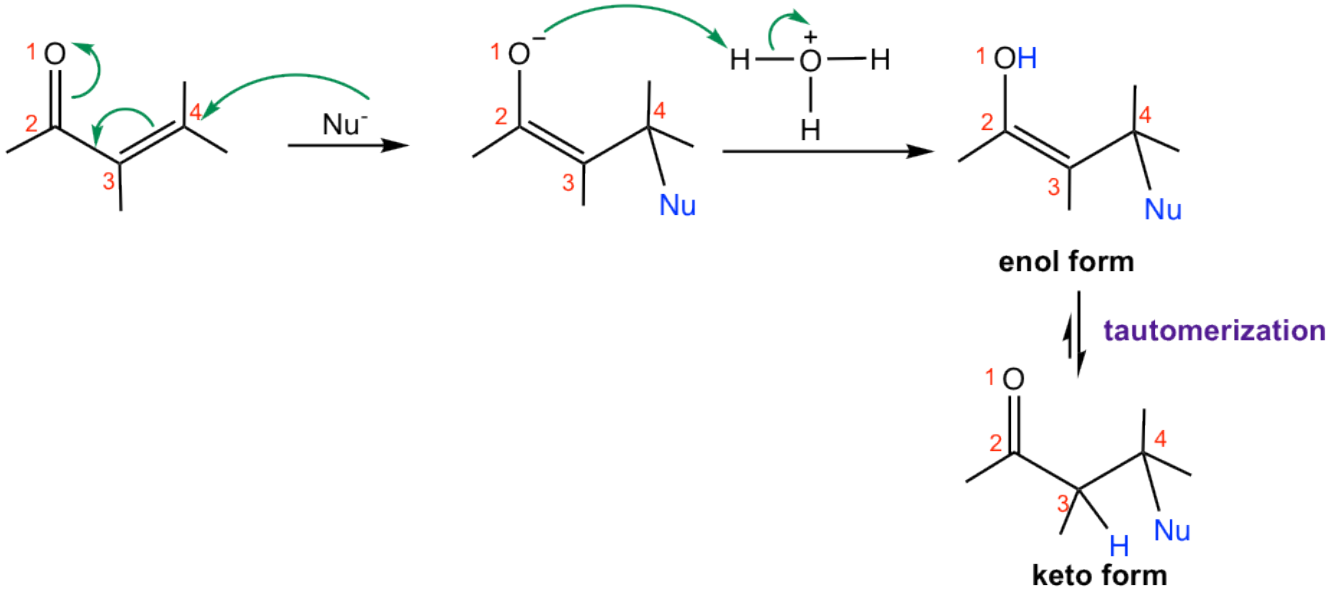


Fig. 6.5e The mechanism for 1,4-addition of α,β-unsaturated compounds

6.5.3 Organocuprate Addition

Here we will introduce a type of new organometallic reagent, organocuprate, that allows 1,4-addition to α,β-unsaturated aldehydes and ketones. An example is given here that the ethyl group is added to the β-carbon of 2-cyclohexen-1-one.

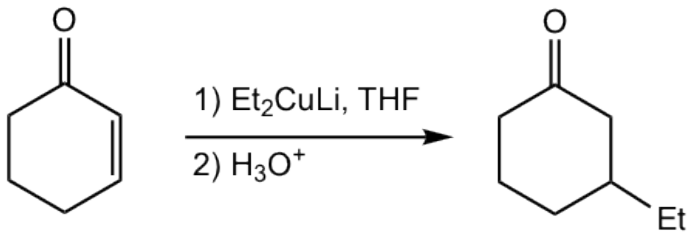


Fig. 6.5f 1,4-addition of organocuprate (lithium diethylcopper) to 2-cyclohexenone

The specific organocuprate reagent applied here is lithium dialkylcopper (R_2CuLi). It is the source of nucleophiles similar to Grignard and organolithium reagents, however, with slightly weaker reactivity, and adds to α,β-unsaturated aldehydes and ketones in the 1,4-addition pathway.

Organocuprate reagents are made from the reaction of organolithium reagents and copper (I) iodide, CuI.

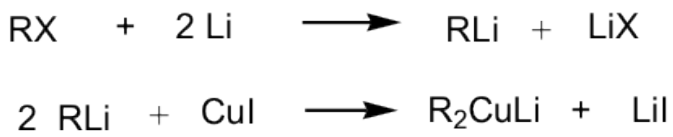


Fig. 6.5g Preparation of organocuprate reagent

While organocuprate provides a way to introduce an alkyl group into the β-carbon, applying organocuprate followed by the alkylation step could introduce **two alkyl groups** into the β-and α-carbons separately, as shown in Fig. 6.5h.

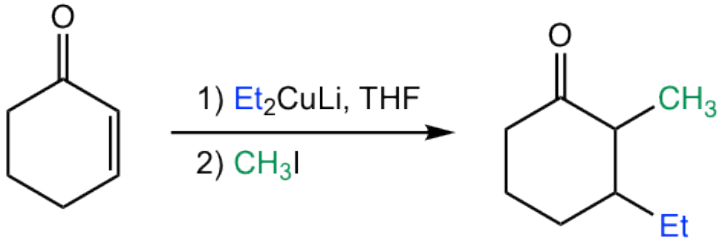


Fig. 6.5h α,β-Dialkylation of α,β-unsaturated compound with organocuprate followed by alkyl halide

The understanding of this reaction comes from the reaction mechanism (Fig. 6.5i).

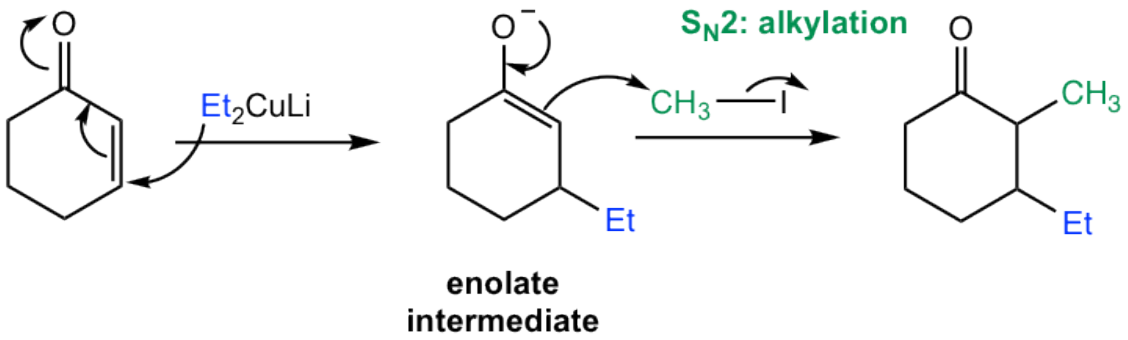
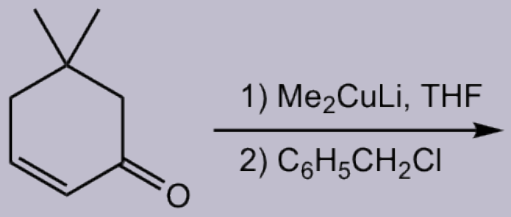


Fig. 6.5i Mechanism for α,β-dialkylation of α,β-unsaturated compound with organocuprate and alkyl halide

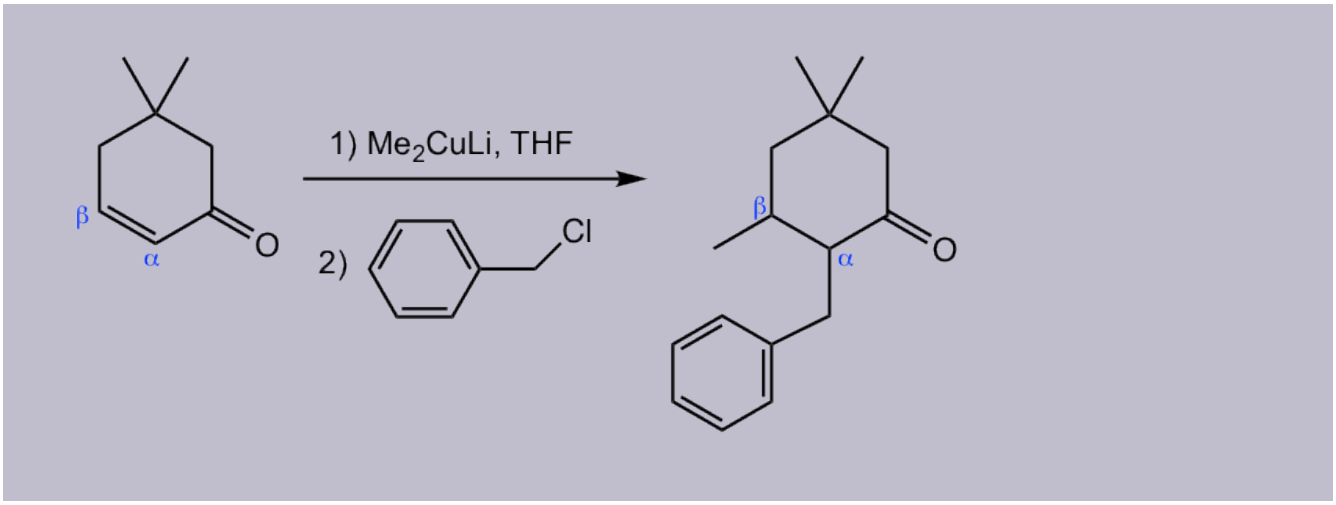
In the first nucleophilic addition step with organocuprate, the enolate intermediate is formed. Instead of protonation as in the common 1,4-addition process, here the enolate reacts with an alkyl halide in an S_N2 reaction in the 2nd step, as we learned in **section 6.3** that enolate is available for alkylation. Overall, the organocuprate reagent followed by alkylation with alkyl halide is a method to achieve **α,β-dialkylation** (the two alkyl groups could be either the same or different) to α,β-unsaturated aldehydes and ketones, and therefore has great applications in synthesis.

Examples

Show the product of the following reaction.



Answer:



6.5.4 Michael Addition

Michael addition is the 1,4-conjugate addition of enolate ion to α,β-unsaturated carbonyl compound. Enolate ion acts as the nucleophile in Michael addition.

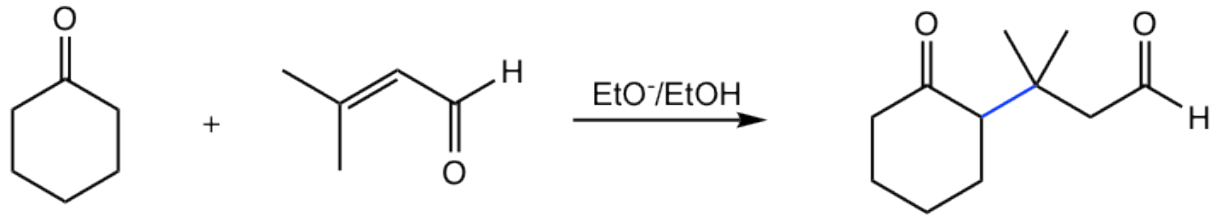


Fig. 6.5j Example of the Michael addition

The mechanism for Michael addition follows the general way of 1,4-addition, with enolate acting as the nucleophile, as shown in Fig. 6.5k. Enolate attacks the β-carbon (C-4) first, and then the protonation with the solvent of the enolate intermediate gives the final product. Alkoxide, RO^-, is the base commonly used for Michael addition to generate enolate, together with the corresponding alcohol ROH as solvent.

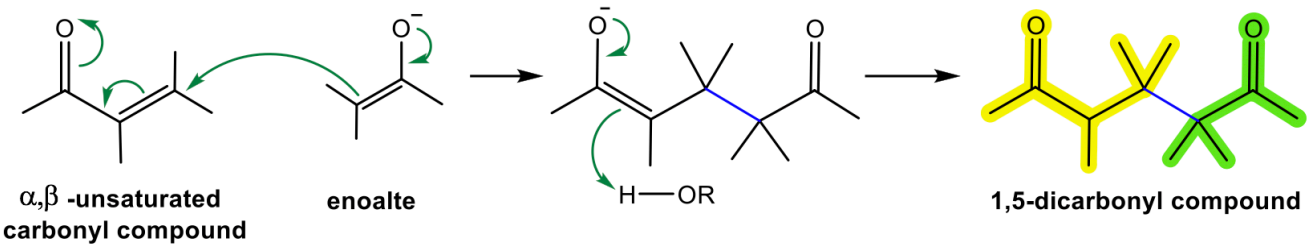


Fig. 6.5k General mechanism for Michael addition

Michael addition is an effective way to build larger molecules by connecting two structure units with a new C-C bond (blue bond in Fig. 6.5k). When Michael addition takes place between the enolate of an aldehyde or ketone with α,β-unsaturated aldehyde or ketone, the 1,5-dicarbonyl compound is formed as a product.

Michael addition takes place with a variety of other reagents as well, as the examples shown in the following table, demonstrate the diverse applications of Michael addition in synthesis.

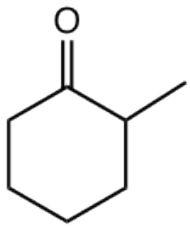
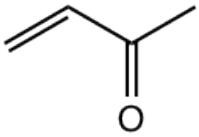
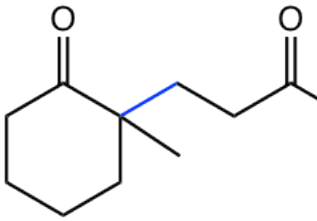
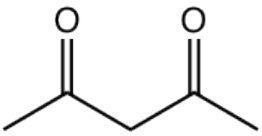
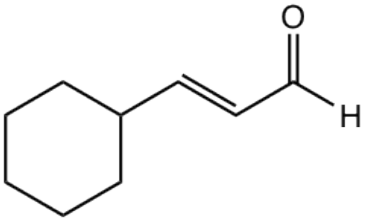
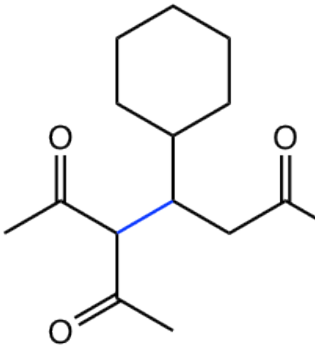
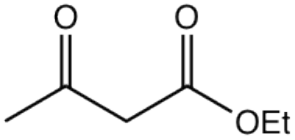
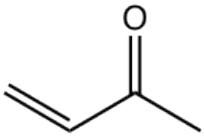
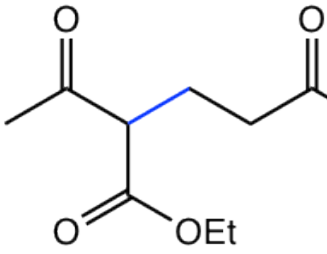
Compound for enolate	α,β-unsaturated compound	Michael addition product
1) 		
2) 		
3) 		

Table 6.1 Examples of Michael addition with a variety of compounds that generate enolates

As you may have noticed in the last two examples in Table 6.1, the compounds to generate enolate are not the usual aldehyde or ketone. These two examples represent a type of compound called β-dicarbonyl compound. The uniqueness of β-dicarbonyl compound is that the hydrogens on the carbon between the two carbonyl groups are even more acidic than α-hydrogens in the carbonyl compound with one C=O group. The pKa of several types of β-dicarbonyl compounds, in the range of 9 ~ 13, are shown in Fig. 6.5l.

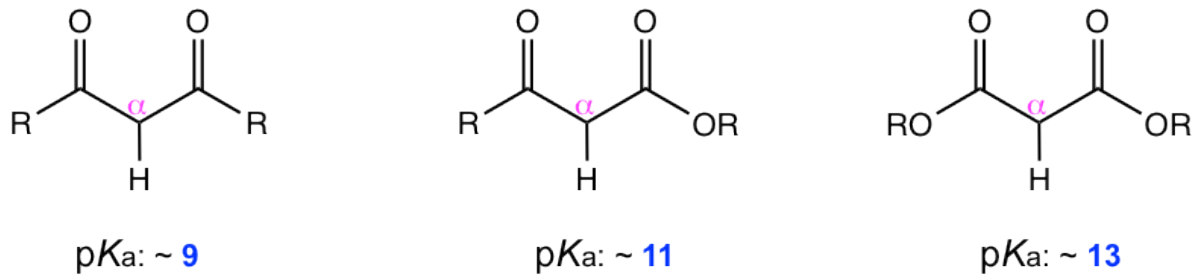


Fig. 6.5l pKa range of α-hydrogens in β-dicarbonyl compounds

The reason for the greater acidity of α-hydrogens in β-dicarbonyl compounds is apparently due to the presence of another C=O bond. The delocalization of negative charge onto two oxygen atoms instead of one helps to stabilize the enolate significantly (Fig. 6.5m), therefore making the hydrogens more acidic.

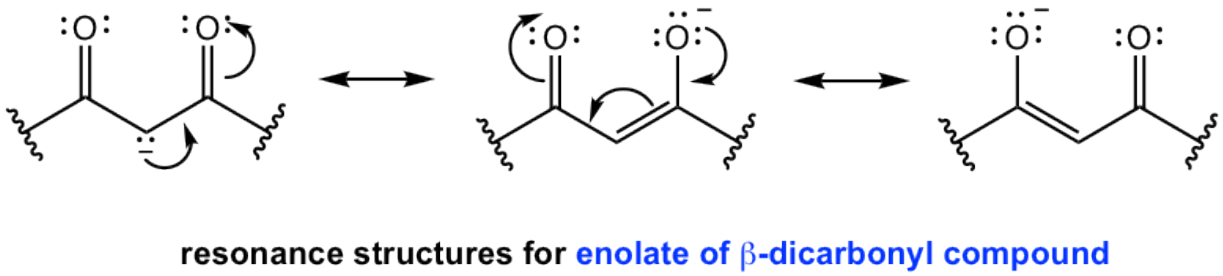


Fig. 6.5m Enolate of β-dicarbonyl compounds stabilized by resonance effect

The stabilized enolates of β-dicarbonyl compounds are used broadly in organic synthesis, and we will see more applications in Chapter 8. Two specific compounds are particularly important and need our attention, they are acetoacetic ester and diethyl malonate.

Fig. 6.5n Structure of ethyl acetoacetate and diethyl malonate

6.5.5 Robinson Annulation

The Michael addition followed by an intramolecular aldol condensation is called **Robinson annulation.** The term annulation means ring-forming because a ring is formed by intramolecular aldol condensation. The product of a 5- or 6-membered ring is usually formed in Robinson annulation because of the stability of the ring.

For the first example in Table 6.1, the product undergoes further intramolecular aldol reaction and gives a bicyclic product, and the overall reaction is a Robinson annulation.

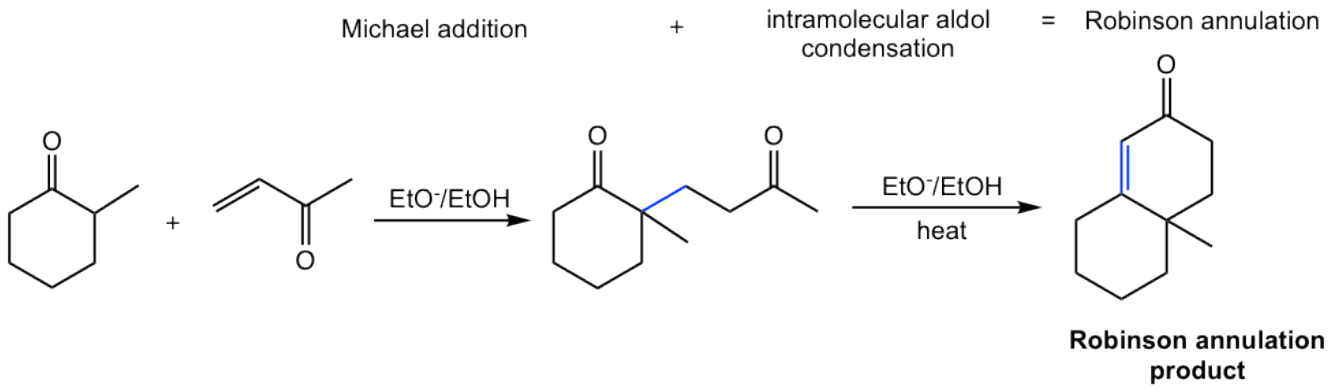
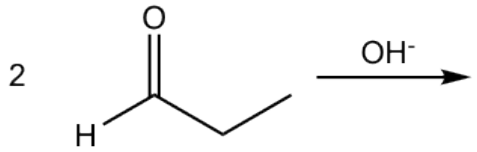


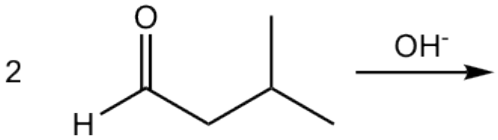
Fig. 6.5o The Robinson annulation reaction example

6.6 Practices

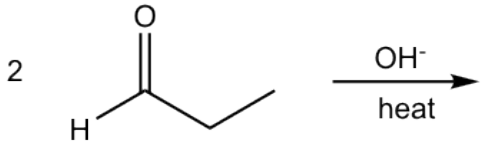
1. Show the major product(s) of the following reactions.

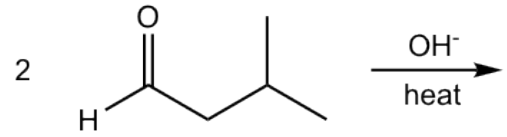
a. Aldol addition



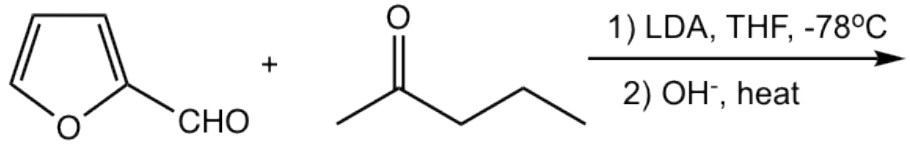


b. Aldol condensation

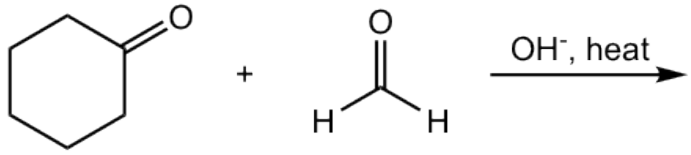




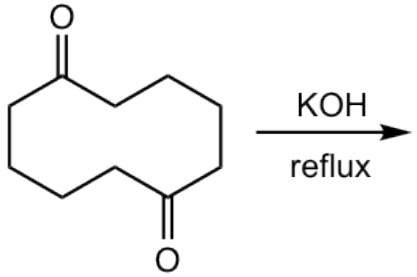
c.



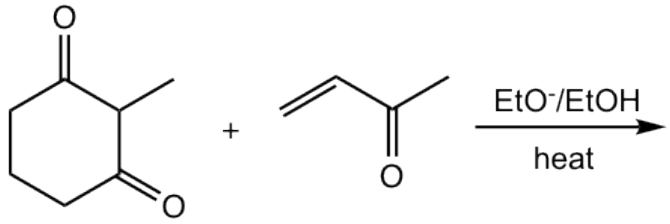
d.



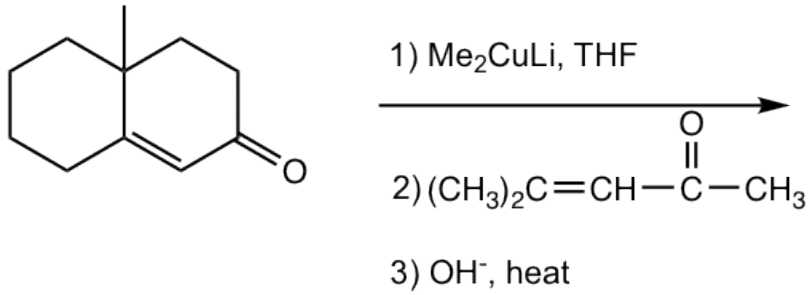
e.



f.

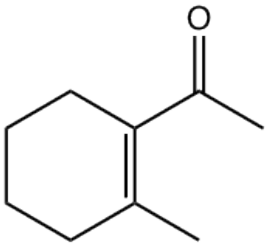


g.

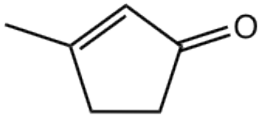


2. Show the structure of the starting compound to prepare the following product.

a)



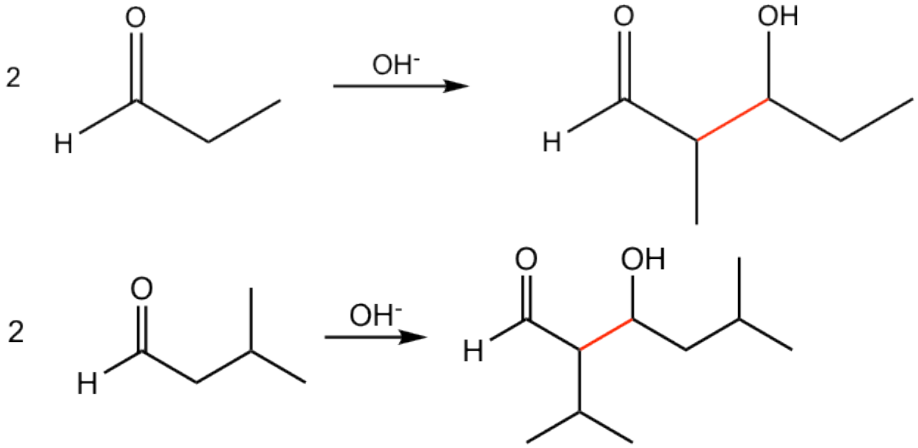
b)



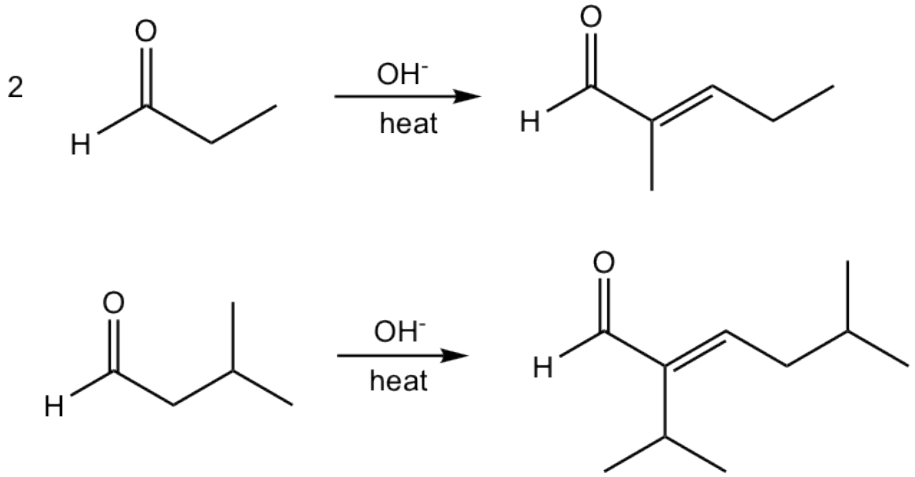
6.7 Practices Answers

1. Show the major product(s) of the following reactions.

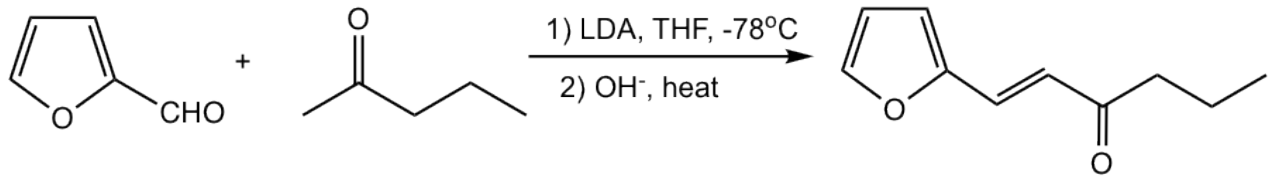
a. Aldol addition



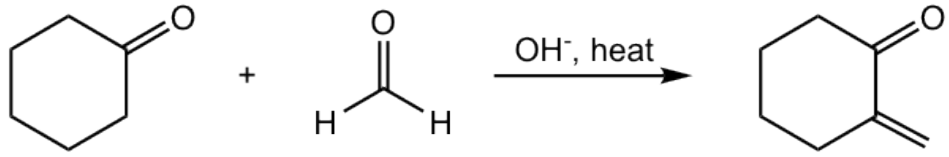
b. Aldol condensation



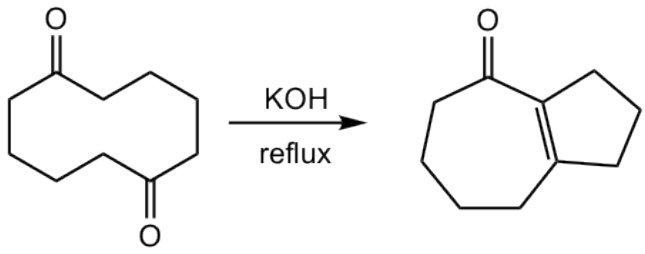
c.



d.



e.



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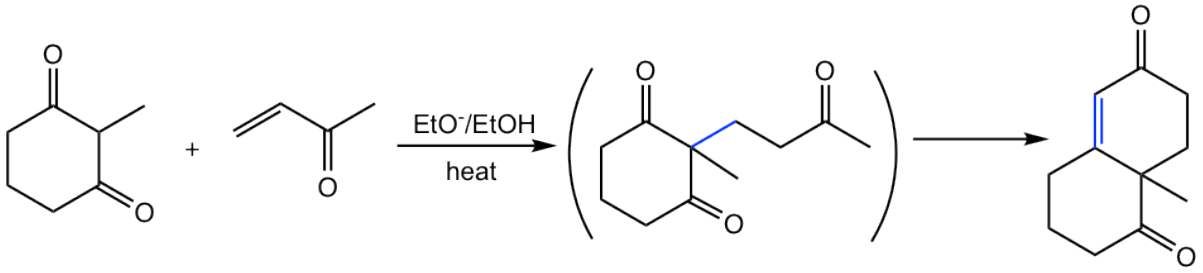
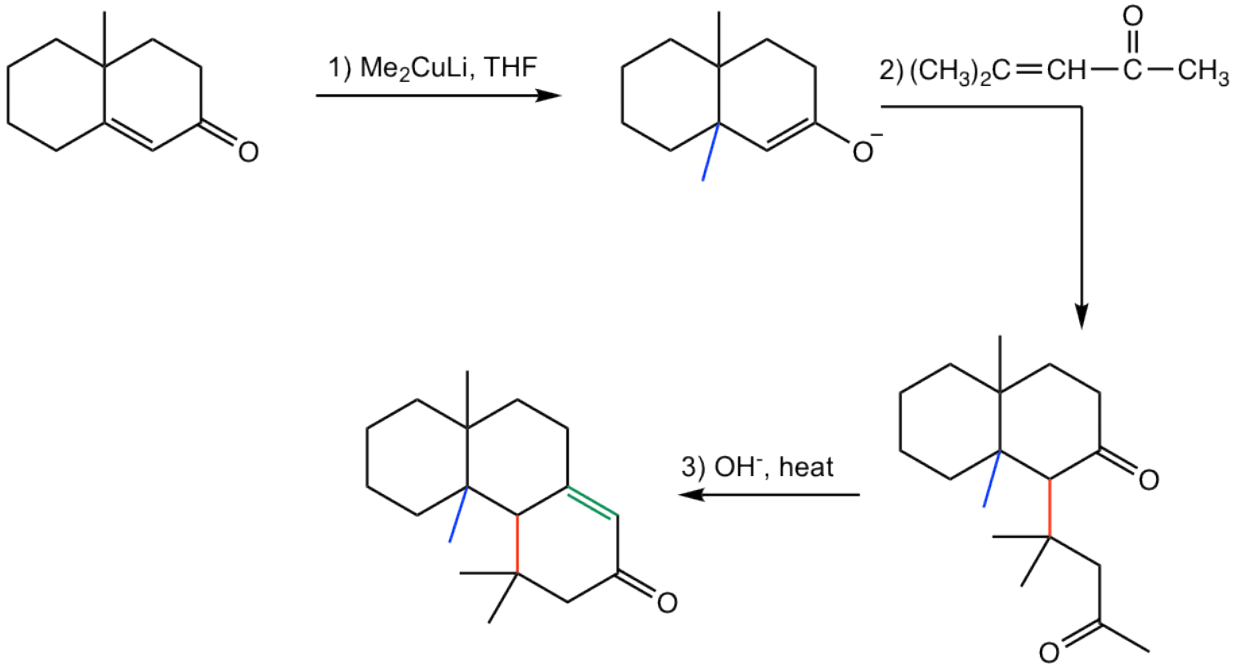
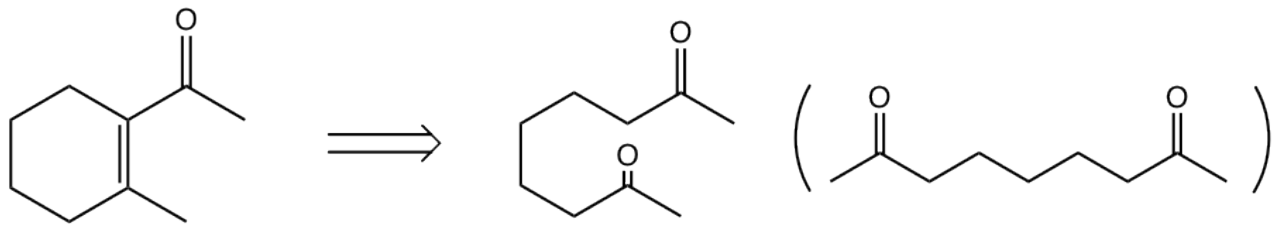


g.

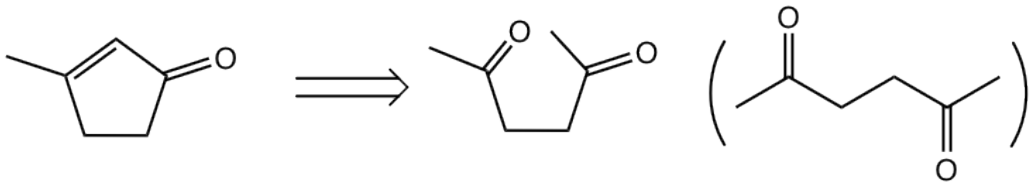


2. Show the structure of the starting compound to prepare the following product.

a)



b)



CHAPTER 7: CARBOXYLIC ACID AND DERIVATIVES

Carboxylic acid is the type of compound that contains a carboxyl group (COOH, or CO2H). Not only carboxylic acid is important in chemistry and biochemistry, but it is also the parent structure of a large family of related compounds called **carboxylic acid derivatives**. Carboxylic acid derivatives have similar structures to carboxylic acid (as shown in Fig. 7a), and also share a common pattern in terms of chemical reactivities. The properties and reactions of carboxylic acid and derivatives are the topics of discussion for this chapter.

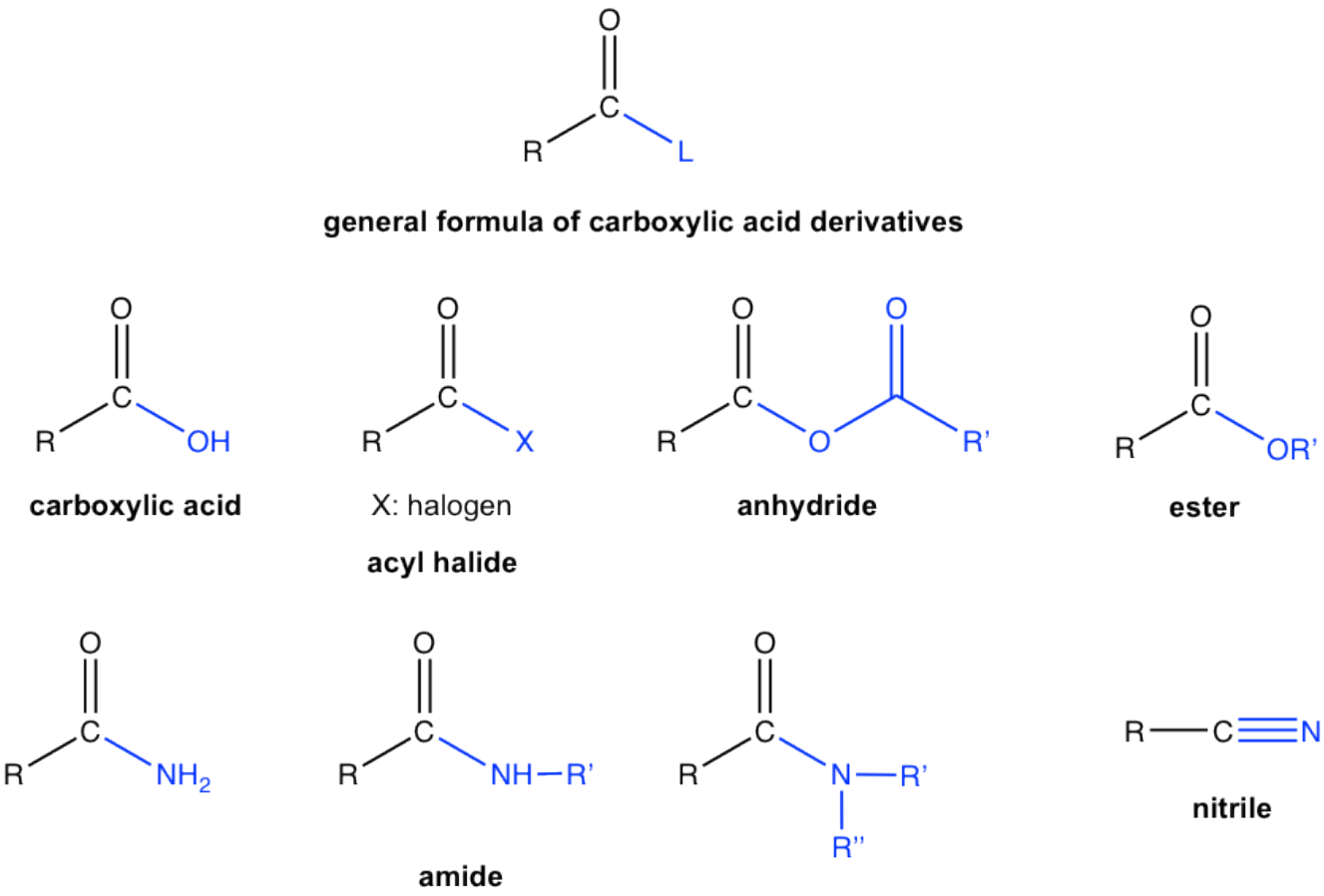


Fig. 7a General structure formula of carboxylic acid derivatives

Nitriles are compounds that contain a C≡N group, called "cyano". They are also considered carboxylic acid derivatives, although the structures do not match the general structure, since they can be converted to carboxylic acids by hydrolysis (**section 7.2.3**).

7.1 Nomenclatures and Physical Properties of Carboxylic Acid Derivatives

In IUPAC nomenclature, a certain suffix is used to indicate a specific functional group as the parent structure of the compound. Two versions of suffixes of each functional group of carboxylic acid or a derivative are listed in Table 7.1. When the functional group is part of the parent carbon chain, the compound is named by replacing the terminal "e" of the hydrocarbon name with the first suffix for that functional group. If the functional group is attached to a ring structure, the second suffix is used by following the name of the ring. Specific examples are given in the table as well for illustration.

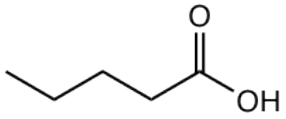
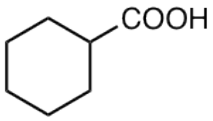
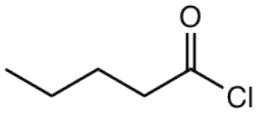
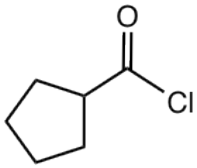
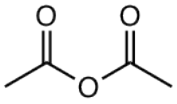
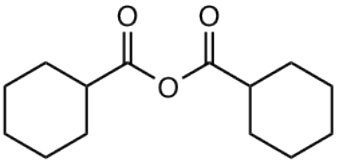
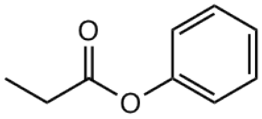
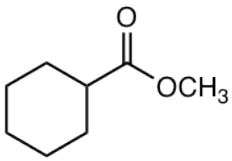
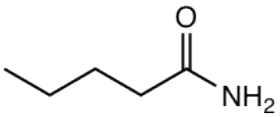
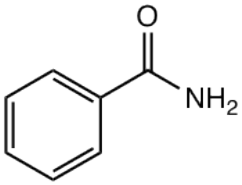
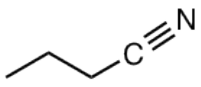
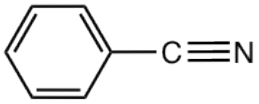
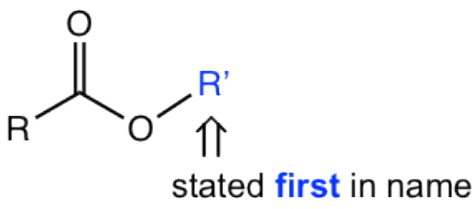
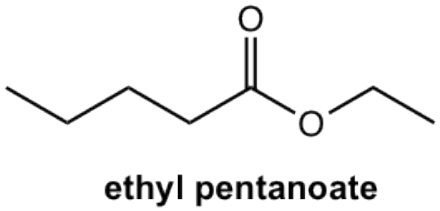
Functional group	Suffix	Examples	
acid	– oic acid – carboxylic acid	 pentanoic acid	 cyclohexanecarboxylic acid
Acyl halide	– oyl chloride – carbonyl halide	 pentanoyl chloride	 cyclopentanecarbonyl chloride
anhydride	– oic anhydride – carboxylic anhydrate	 ethanoic anhydride (acetic anhyride)	 cyclohexanecarboxylic anhydride
ester	– oate – carboxylate	 phenyl propanote	 methyl cyclohexanecarboxylate
amide	– amide – carboxamide	 pentanamide	 benzenecarboxamide
nitrile	– nitrile – carbonitrile	 butanenitrile (keep the “e”)	 benzenecarbonitrile

Table 7.1 Carboxylic acid derivatives suffix and examples

There are several extra notes about the naming of carboxylic acid derivatives, with an example given for each case.

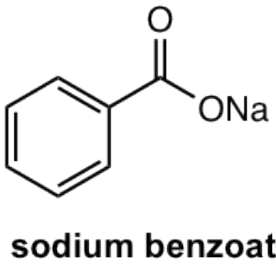
Name of Ester





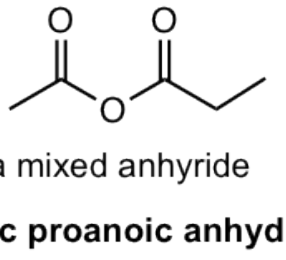
For the naming of an ester, the name of the alkyl group attached to the carboxyl oxygen is stated first, followed by the name of the acid with the proper suffix.

Name of Salts



Salts of carboxylic acids are named with the same suffix as ester, that is “oate”, with the name of the metal put first.

Name of Anhydride, symmetric and mixed

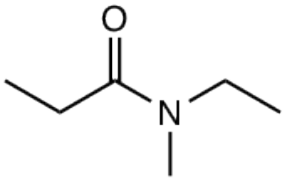


An acid anhydride is the functional group generated by the loss of water from two carboxylic acid molecules (section ?? for details). If the two acids are the same, the anhydride is symmetric. If they are different, the anhydride is a

mixed anhydride. The mixed anhydride is named by starting the name of both acids in alphabetical order, followed by "anhydride".

Amide with substituents on Nitrogen

For amide, if a substituent is bonded to the nitrogen, the name of the substituent is stated first, preceded by a capital N, then followed by the name of the amide.



***N*-ethyl-*N*-methylpropanamide**

Properties of Carboxylic Acids and their Derivatives

Carboxylic acid is a type of organic acid with pK_a in the range of about 5 (**section 3.3 in Book I**). Carboxylic acid reacts with the solution of sodium hydroxide readily to form the sodium salt.

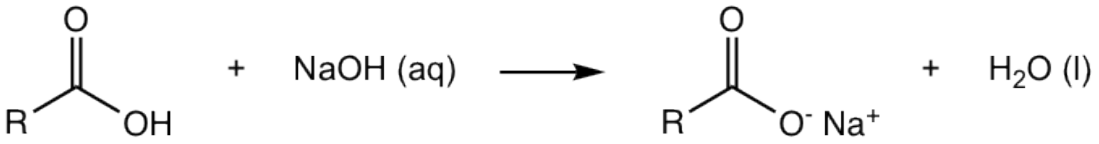


Fig. 7.1a Reaction of carboxylic acid with sodium hydroxide

The presence of the electron-withdrawing group increases the acidity of carboxylic acid (**section 3.4.3 in Book I**) since those groups help to delocalize the negative charge of the conjugate base and make the conjugate base more stable.

The boiling point of carboxylic acid is generally much higher than that of ester or acyl chloride with a similar molar mass, because of the hydrogen bonds between each other (Fig. 7.1b).

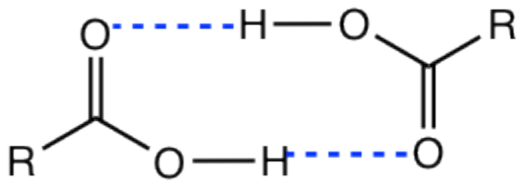


Fig. 7.1b Hydrogen bonds between carboxylic acid molecules

The carboxylic acid can also form hydrogen bonds with water, therefore the low-molecular mass carboxylic acids (up to four carbons) show appreciable solubility in water. Water solubility decreases with the length of the carbon chain increases.

Other Common Carboxylic Acids and Derivatives

Carboxylic acids and esters are found widely in nature. The most well-known one is acetic acid, the ingredient in vinegar. (S)-Lactic acid is the compound responsible for the burning feeling of muscle after work out. Citric acid occurs naturally in citrus fruit, for example, lemons have the highest concentration and oranges have less. Some green leafy vegetables, such as spinach, are rich in oxalic acid. Maleic acid (Z isomer) and fumaric acid (E isomer) are the geometric isomers of butenedioic acid, that are both naturally present in honey. The structures of these common acids are shown in Fig. 7.1c.

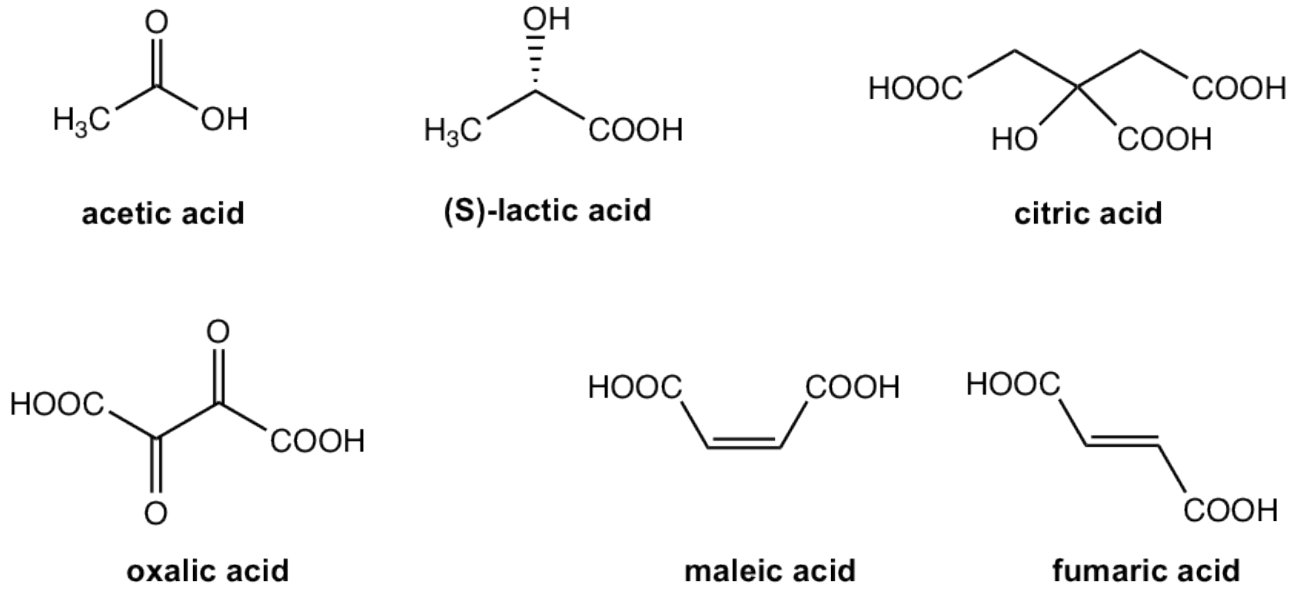


Fig. 7.1c Common carboxylic acids

The pleasant odors of many flowers and fruits are due to esters, as shown in Fig. 7.1d. Without hydrogen atoms bonded to oxygen, esters cannot form hydrogen bonds, therefore the boiling points of esters are lower than that of acids with comparable molar mass.

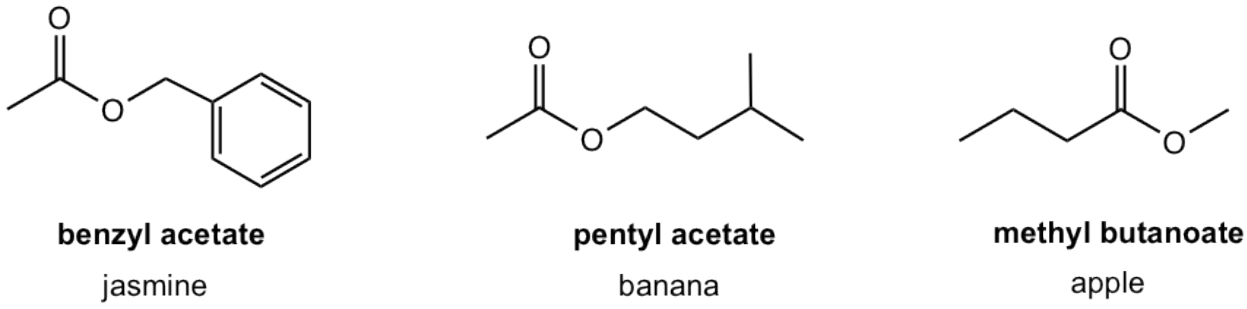


Fig. 7.1d Examples of esters with pleasant odors

Amide is the key functional group that forms the backbone of peptides and proteins.

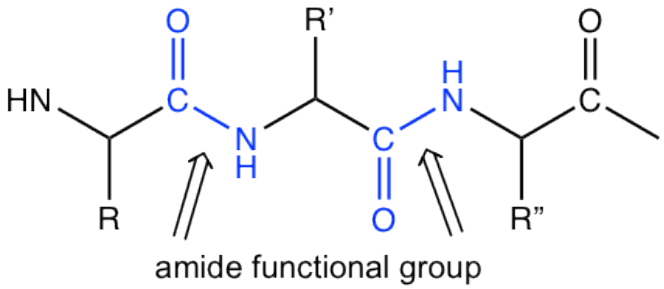


Fig. 7.1e General structure for a peptide

For the structure of amide, the resonance structure with charge separation makes a greater contribution to the hybrid than other derivatives, because the nitrogen atom can better accommodate a positive charge. Because of this reason, dipole-dipole force applies to amide molecules, which explains the high boiling points of amides. In addition, hydrogen bonds form for amides with NH or NH_2 group, which also contributes to the high boiling points.

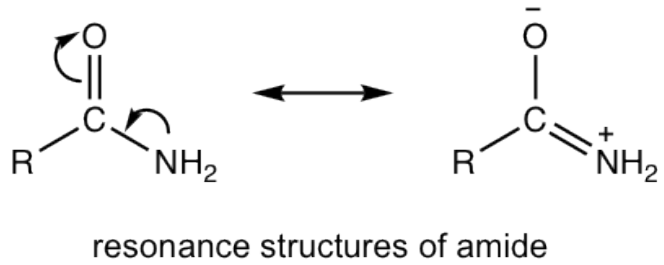


Fig. 7.1f Resonance structures of amide

7.2 Preparation of Carboxylic Acid

The methods to prepare carboxylic acids can be generally divided into three categories: oxidation reaction, Grignard reaction and hydrolysis of nitrile.

7.2.1 Preparation of Carboxylic Acid by Oxidation

Since the carboxyl group COOH is in the high oxidation state, it can be prepared by oxidation of other functional groups in the lower oxidation states, for example, alkene, alcohol, and aldehyde (refer to **section 10.7 in Book I**, for oxidation states of organic compounds). We have learned all these oxidation reactions in earlier sections, summaries are provided here.

Oxidation of Alkenes (refer to section 10.7 in Book I)

The oxidative cleavage of C=C double bond with potassium permanganate, $KMnO_4$, under hot basic conditions, could produce the (salt of) carboxylic acid if the structure of the alkenes is appropriate.

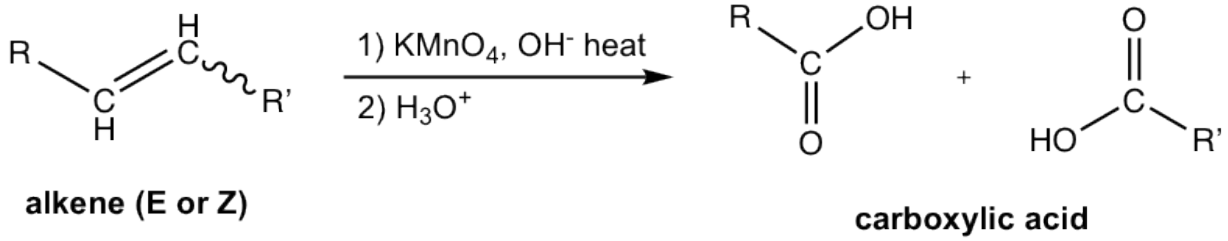


Fig. 7.2a Preparation of carboxylic acid by oxidation of alkene

For symmetric alkenes (R and R' are the same), only one carboxylic acid is generated as a product and this method can be applied effectively for preparation.

Oxidation of Primary Alcohols and Aldehydes (refer to section 1.2.5)

When primary alcohols are oxidized by potassium permanganate $KMnO_4$ in basic condition, (salt of) carboxylic acid is produced. Under the acidic condition with Cr (VI) reagents (CrO_3, or H_2CrO_4), primary alcohols are oxidized to aldehydes first, then to carboxylic acids as final products.

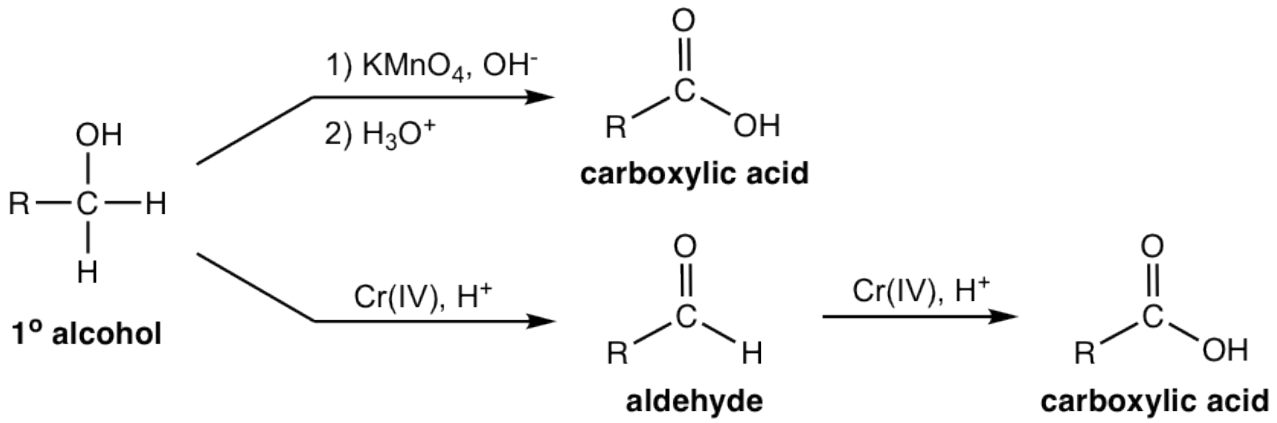


Fig. 7.2b Preparation of carboxylic acid by oxidation of alcohol

Oxidation of alkylbenzenes (refer to section 5.3.2)

The alkyl group (the group must have the hydrogen in the benzylic position) attached to a benzene ring is oxidized to carboxylic acid by potassium permanganate $KMnO_4$ in basic condition, or sodium dichromate $Na_2Cr_2O_7$ in acidic solutions.

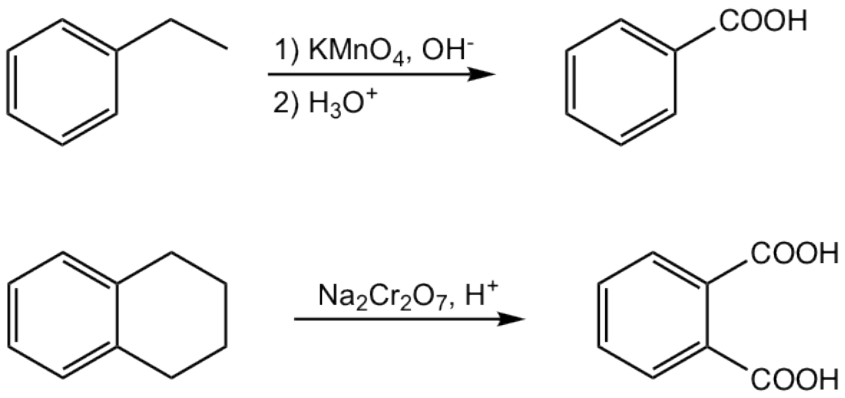


Fig. 7.2c Preparation of benzylic acid by oxidation of alkylbenzene

7.2.2 Preparation of Carboxylic Acid by Grignard Reaction with CO_2 (refer to section 1.5.4)

The reaction between Grignard reagent and carbon dioxide (CO_2), followed by acidic work-up, produces carboxylic acid. Since Grignard reagents are compatible with a variety of groups, this method can be used to synthesize carboxylic acid with a variety of different structures.

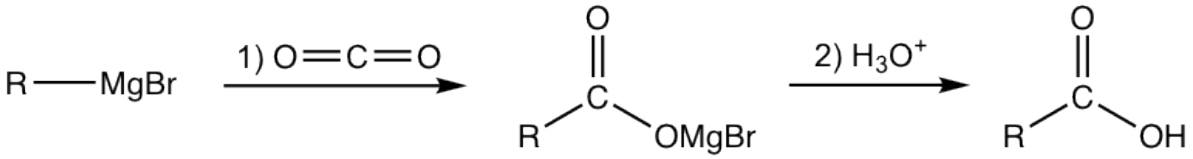


Fig. 7.2d Preparation of carboxylic acid by Grignard reaction with carbon dioxide

7.2.3 Preparation of Carboxylic Acid by Hydrolysis of Nitrile

As mentioned nitriles are considered carboxylic acid derivatives because they can be converted to carboxylic acid by hydrolysis. Nitriles can be prepared by either the S_N2 reaction of halides with sodium cyanide, or the addition of aldehyde with sodium cyanide followed by protonation.

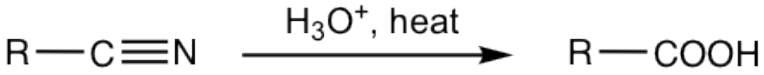


Fig. 7.2e Hydrolysis of nitrile to carboxylic acid

A specific example is given here:

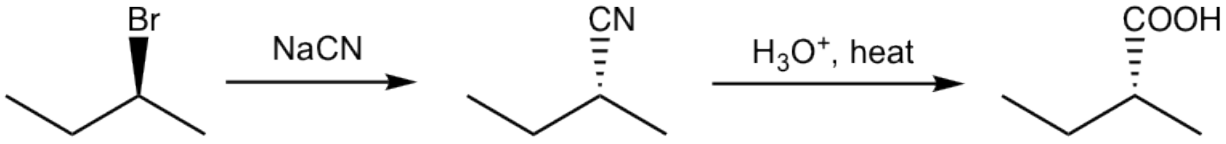


Fig. 7.2f Example of preparation of carboxylic acid by nitrile

7.3 Reactions of Carboxylic Acid and Derivatives: Nucleophilic Acyl Substitution

7.3.1 Two Categories of Carbonyl Compounds

The reactivity of carboxylic acid and derivatives still focuses on the carbonyl group, specifically on the electrophilic carbon because of the polarity of the C=O bond. The carbonyl group together with the R (or Ar) group attached is called the **acyl group**.

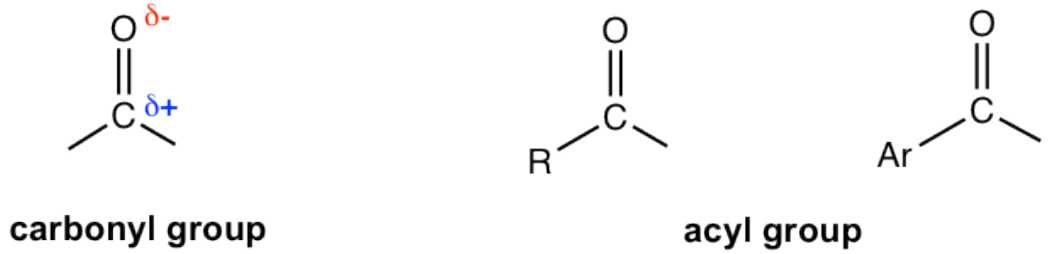


Fig. 7.3a Structure of carbonyl group and acyl group

The above structures might remind you of aldehydes and ketones, which also contain the acyl group. Aldehydes and ketones, and carboxylic acids and derivatives are all carbonyl compounds since they all have the carbonyl group. However, they belong to two categories in terms of reactivity because the other group that is attached to the acyl group strongly affects the reactivity of the carbonyl compounds (Fig. 7.3b).

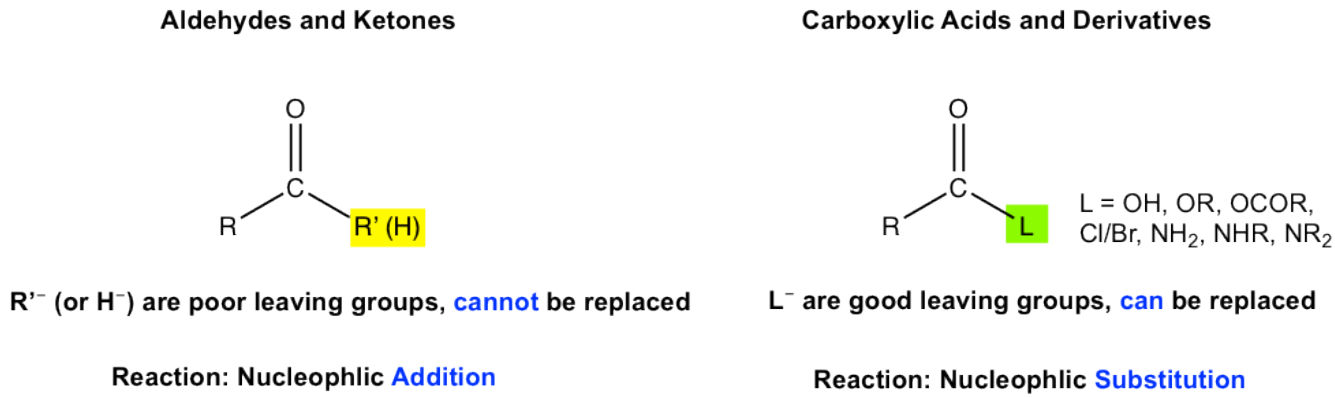

Aldehydes and Ketones
Carboxylic Acids and Derivatives
R'⁻ (or H⁻) are poor leaving groups, cannot be replaced
L⁻ are good leaving groups, can be replaced
L = OH, OR, OCOR, Cl/Br, NH2, NHR, NR2
Reaction: Nucleophilic Addition
Reaction: Nucleophilic Substitution

Fig. 7.3b Comparison between two categories of carbonyl compounds

In aldehydes and ketones, the acyl group is attached to hydrogen or alkyl group (H or R) that are poor leaving groups and **cannot** be replaced by another group. In carboxylic acids and derivatives, the acyl group is attached to a group that contains the electronegative atom (OH, OR, Cl, NH_2, etc), these groups are good (or reasonably good) leaving groups

and **can** be replaced by another group. As a result, (nucleophilic) **addition is the common reaction for aldehydes and ketones** (Chapter 2), but **carboxylic acids and derivatives usually undergo (nucleophilic)substitution** instead.

7.3.2 General Mechanism of Nucleophilic Acyl Substitution

The substitution reaction of carboxylic acids and derivatives is generally called **acyl substitution** because it takes place on the acyl group. It is not a one-step substitution though, but goes through the addition-elimination mechanism.

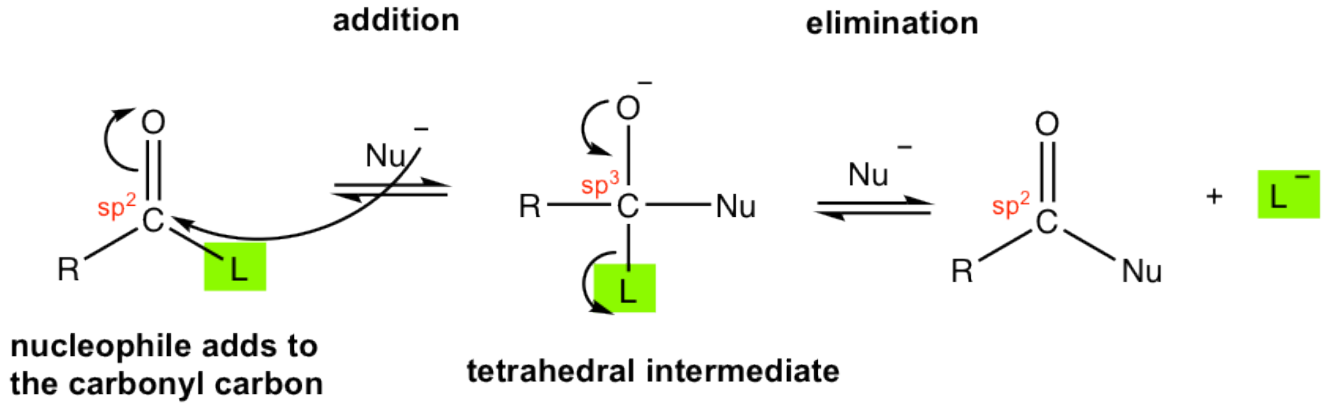


Fig. 7.3c General Reaction Mechanism of Acyl Substitution with a Negatively Charged Nucleophile

The mechanism in Fig. 7.3c represents the acyl substitution process with a negatively charged nucleophile. (If a neutral nucleophile reacts, there will be extra proton transfer steps, refer to **section 7.5**). In the above mechanism, the nucleophile first attacks the carbonyl carbon that bears the partial positive charge, and forms an intermediate. The intermediate is called a **tetrahedral intermediate** because the central carbon is the sp^3 hybridized carbon in a tetrahedral shape. In the tetrahedral intermediate, both group L and the nucleophile contain electronegative atoms, for example, O or N, and therefore are very unstable. The group L leaves in the second step and another π bond is reformed to give the final product, in which the nucleophile replaces the group L.

Both steps in the above mechanism are reversible, which means the reaction has the chance to go backward as well. Whether the forward or the backward reaction is predominant in the equilibrium depends on the relative basicity (or leaving ability) between group L and the nucleophile. As we learned before in the S_N1/S_N2 reaction (**section 7.3 in Book I**), the weaker the base the better it is as a leaving group. Therefore, if L^- is a weaker base than Nu^-, i.e. L^- is a better leaving group than Nu-, the reaction proceeds in the forward direction and produces the desired substitution product. On the other side, if Nu^- is a weaker base (or a better leaving group) than L^-, then the backward reaction predominates and it is not productive to carry out the reaction.

7.3.3 Relative Reactivity of Carboxylic Acid and Derivatives

Different carboxylic acid derivative has different reactivity towards acyl substitution reaction. In general, the order of reactivity is:

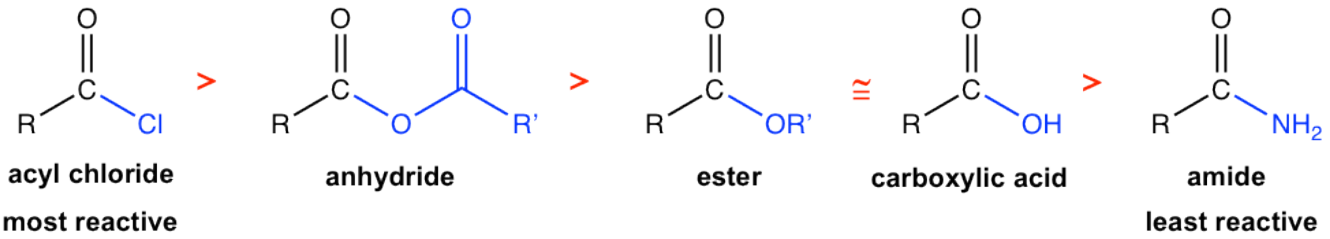


Fig. 7.3d Relative reactivity of carboxylic acid derivatives toward acyl substitution

Acyl chlorides are the most reactive, and amides are the least reactive towards acyl substitution. As was discussed in the previous section the better the leaving group L, the more easily the acyl substitution takes place. So the relative reactivity of carboxylic acid derivatives could be rationalized by the leaving group ability of the group L, or the basicity of L^-, in different derivatives. The weaker the basicity of L^-, the better the leaving group is, and the more reactive the carboxylic acid derivative. The order of the basicity of leaving groups is shown below which matches the order of reactivity.

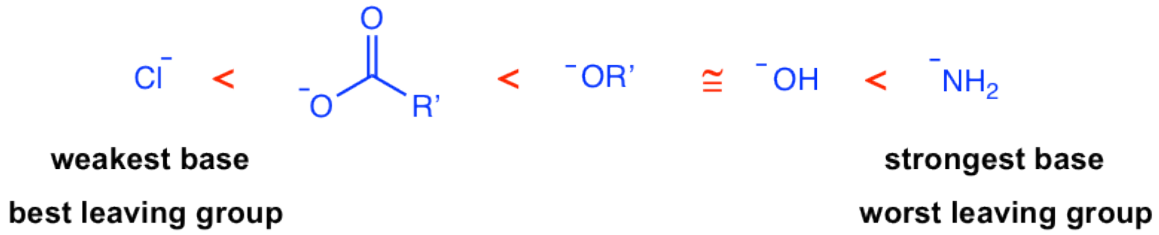


Fig. 7.3e Order of basicity and leaving group properties of group L in carboxylic acid derivatives

An important conclusion that arises from the relative reactivity listed above is that ***a more reactive carboxylic acid derivative can be converted into a less reactive derivative in a nucleophilic acyl substitution, but the reverse process is usually more difficult and requires special reagents when possible.*** This is because in the acyl substitution, the leaving group has to be a weaker base than the nucleophile. As a result, the most reactive acyl chloride can be used as a reactant to produce any of the other derivatives. For example, acyl chloride can be converted to an ester (Cl^- is a weaker base than RO^-), but the ester cannot be converted into any acyl chloride. The application of this trend in the synthesis of carboxylic acid derivatives is that the **less reactive derivative can be prepared from the more reactive derivative, but not the other way**.

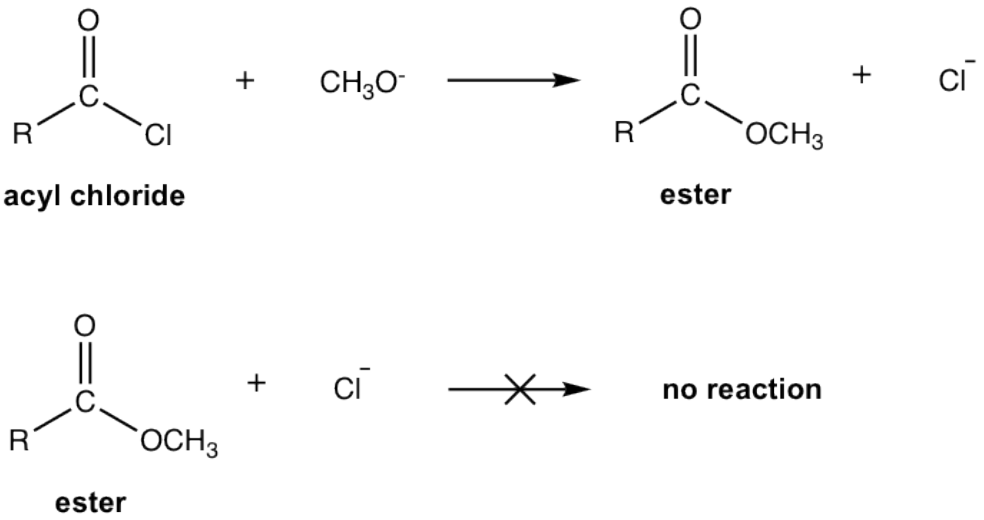


Fig. 7.3f Acyl chloride can be converted to ester but not the other way

Further discussions on the properties and reactions of each functional group are in the following sections.

7.4 Acyl Chloride and Carboxylic Acid Anhydrides

7.4.1 Preparations of Acyl Halides

Acyl halides are the most reactive of the carboxylic acid derivatives, as a result, they cannot be prepared from any other derivatives. To prepare acyl halides, other special reagents will be needed. Thionyl chloride ($SOCl_2$), phosphorus trichloride (PCl_3), and phosphorus tribromide (PBr_3) are the reagents used most commonly, and heat is usually required (refer to **section 1.2.3** for application of these reagents to prepare alkyl halides from alcohols).

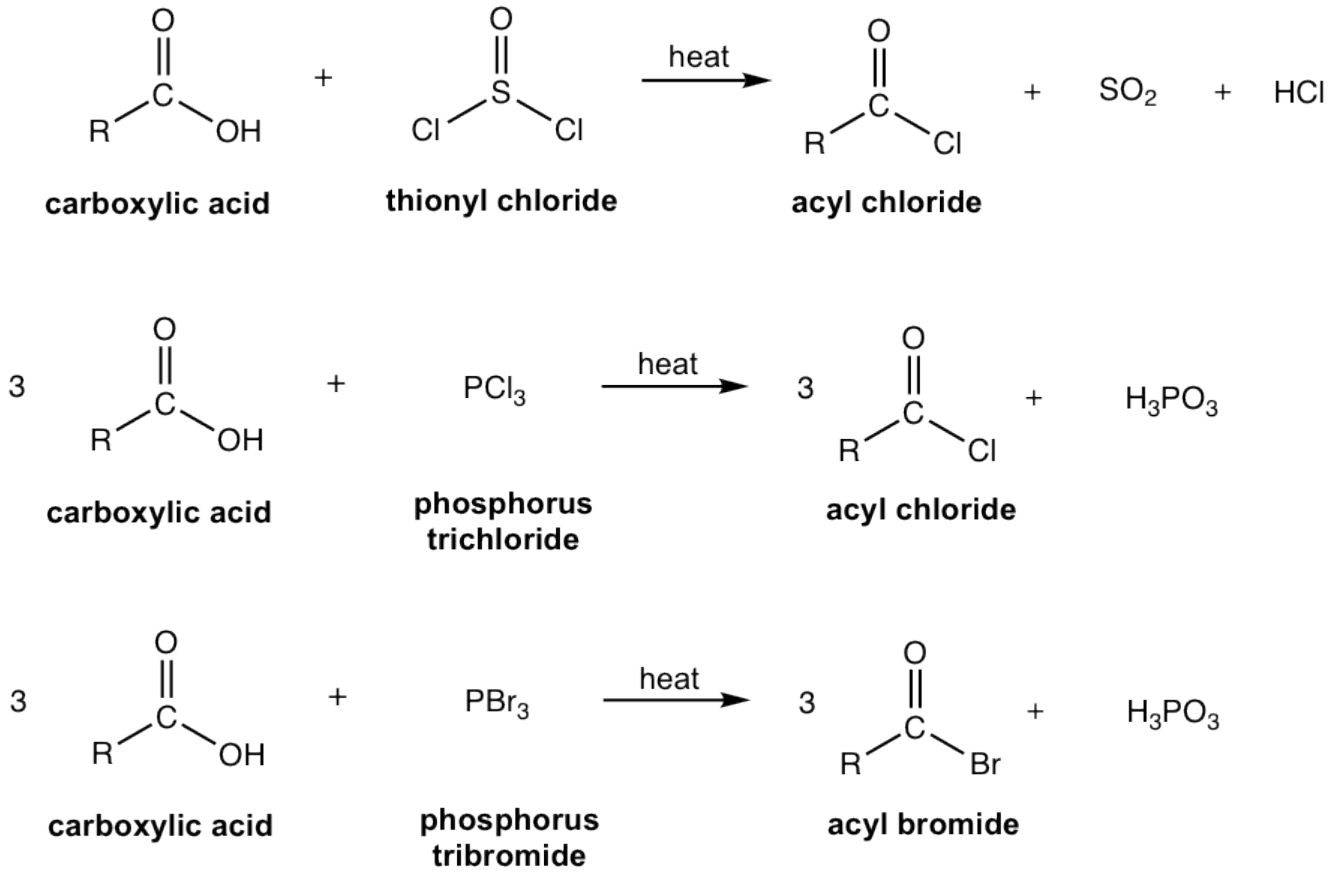


Fig. 7.4a Methods for preparation of acyl chlorides

We will not go through the detailed mechanism for these reactions, however, they all involve nucleophilic addition-elimination process as well.

7.4.2 Preparations of Other Carboxylic Acid Derivatives From Acyl Halides

Since acyl halides are the most reactive, they are readily converted to other less reactive derivatives, as summarized in Fig. 7.4b below. The most effective way to synthesize anhydride, ester, and amide is by using acyl halide as a starting material, because of its high reactivity.

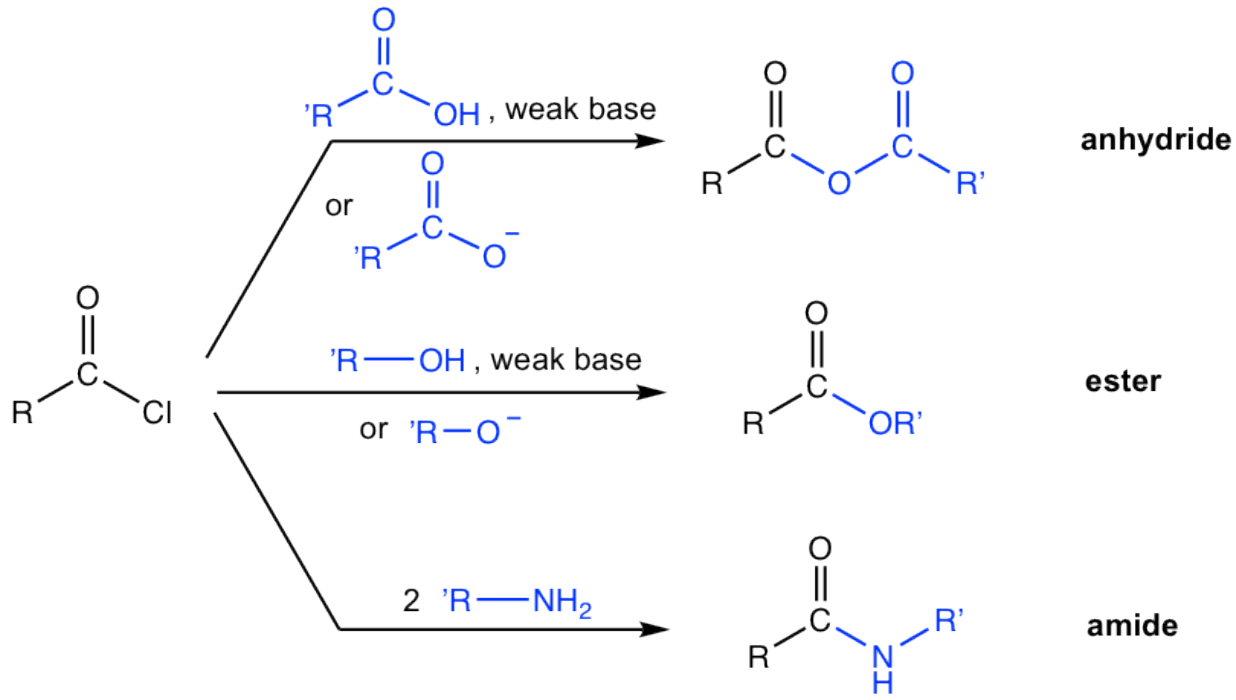


Fig. 7.4b Preparation of anhydride, ester and amide from acyl chloride

A couple of notes for the above reactions:

- Acyl chloride reacts with acid to produce anhydride, and acyl chloride reacts with alcohol to give ester. For these reactions, either a neutral reactant (RCOOH or ROH) or the salt of the reactant ($RCOO^-$ or RO^-) can be used. When salt is used, i.e., with negatively charged nucleophiles, the mechanism follows the general mechanism in **Fig. 7.3c** exactly. When the neutral reactant is applied, a weak base is required to neutralize the by-product HCl and an extra deprotonation step is involved, the mechanism is shown below in Fig. 7.4c with synthesis of ester as the example.

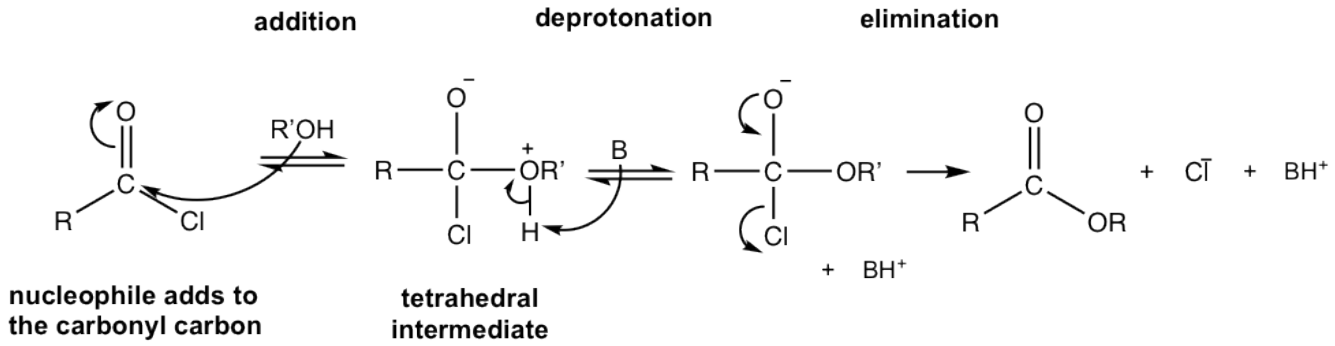


Fig. 7.4c Mechanism for the reaction of an acyl chloride with alcohol to produce ester

- When acyl chloride reacts with an amine, practically two equivalents of amine are required. The extra amount of amine is used to neutralize the by-product HCl, and ensure there will be enough unprotonated amine to react with the acyl halide. A specific example is given below.

7.4.3 Preparation of Carboxylic Acid Anhydrides

As mentioned in the previous section acyl chloride is a great starting compound to produce other derivatives, including anhydride. For the reaction between acyl chloride and an acid to prepare anhydride, amine (for example pyridine) is usually used as the weak base to neutralize the by-product HCl and drive the reaction to completion. Such a reaction is useful to prepare both symmetric anhydrides (R=R') and mixed anhydrides (R≠R').

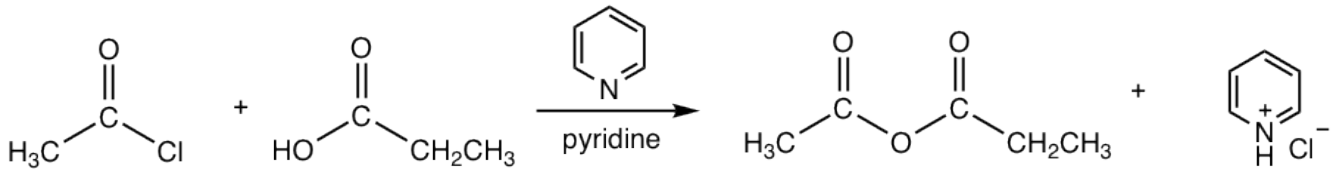


Fig. 7.4d Preparation of ethanoic propanoic anhydride

For dicarboxylic acid, intramolecular dehydration occurs between the two COOH groups by heating, and dicarboxylic acid is converted to cyclic anhydride. The reaction takes place readily when the cyclic anhydride is a five- or six-membered ring. The preparation of maleic anhydride is shown in Fig. 7.4e.

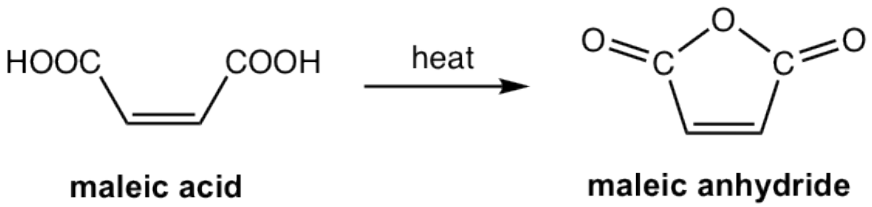


Fig. 7.4e Preparation of maleic anhydride from maleic acid

7.4.4 Preparations of Other Carboxylic Acid Derivatives From Anhydrides

Referring to the relative reactivity of carboxylic acid derivatives (**section 7.3.3**), we can predict that anhydride can be used to synthesize ester and amide, by reacting with alcohol or amine respectively, as shown in the equations below in Fig. 7.4f.

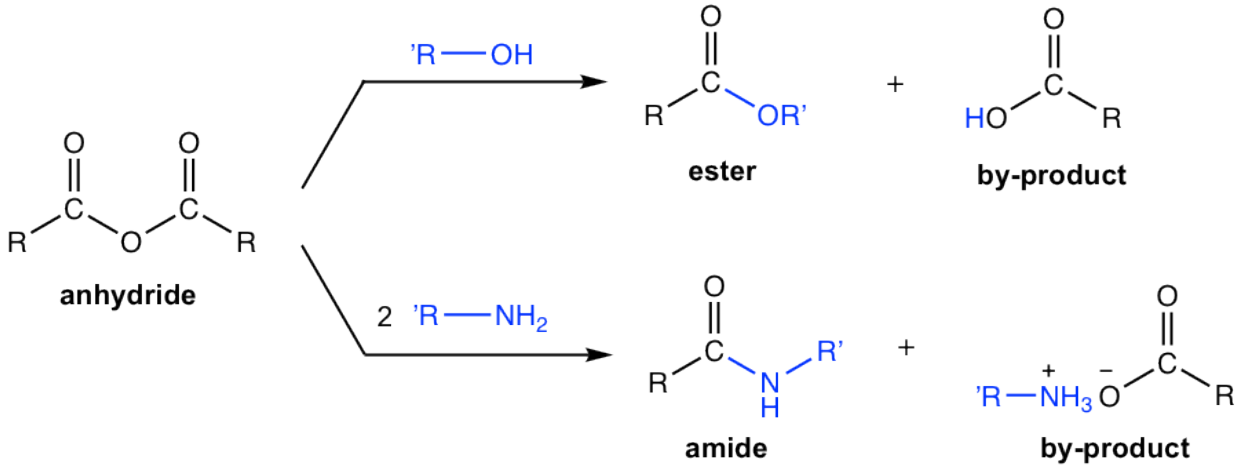


Fig. 7.4f Preparation of ester and amide from anhydride

Please note that when anhydride is used for the synthesis of other derivatives, the organic by-product carboxylic acid (or the salt of carboxylic acid) is always generated.

7.5 Esters

7.5.1 Preparation of Ester

Preparation of Ester from Carboxylic Acid

Esters can be prepared through the reaction between carboxylic acids and alcohols, and the reaction is called **esterification**. Since carboxylic acid is not very reactive towards the acyl substitution, acid is required as a catalyst for esterification.

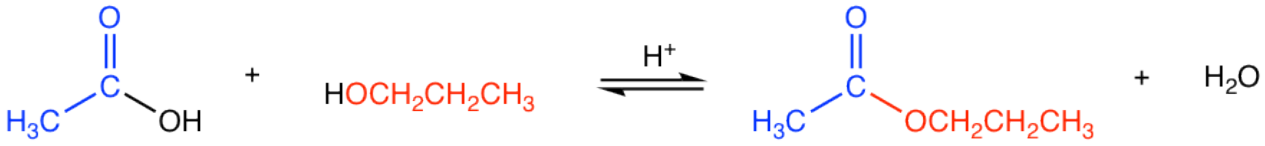


Fig. 7.5a Examples of esterification

The reaction is reversible. Strategies such as using excess acid or alcohol, and removing water from the reaction mixture help to increase the yield of the ester.

The mechanism for acid-catalyzed esterification, which is shown in Fig. 7.5b, still generally follows the nucleophilic addition-elimination process, with a few extra proton-transfer steps though.

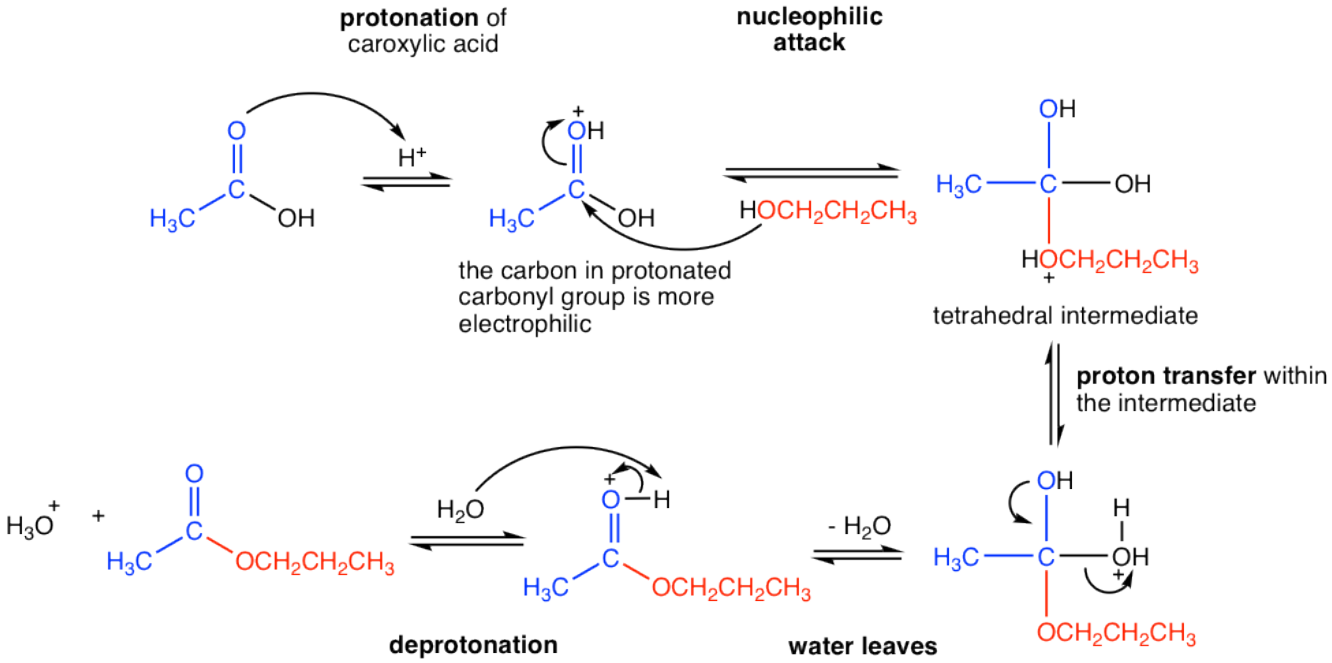


Fig. 7.5b Mechanism for the acid-catalyzed esterification

In the presence of strong acid, the carbonyl group in carboxylic acid is protonated. The carbon of the protonated carbonyl group is more electron-poor (or more electrophilic) and, therefore has higher reactivity towards nucleophilic attack. The neutral nucleophile, alcohol, then attacks the protonated carbonyl group and generates the tetrahedral intermediate. A proton transfer occurs next between the ether oxygen and the alcohol oxygen in the tetrahedral intermediate, then water leaves as the leaving group. A last deprotonation step gives the final neutral ester product. It is also indicated from the mechanism that the OR group (red part in the mechanism) in the ester comes from alcohol, and the acyl group (blue part in the mechanism) is from the carboxylic acid.

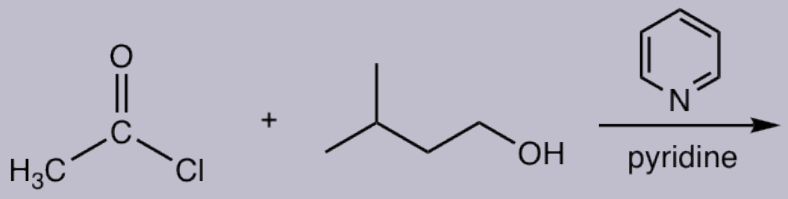
The reverse process of esterification is the acid-catalyzed hydrolysis of ester to produce carboxylic acid and alcohol back. See more discussions about hydrolysis in the next **section 7.7**.

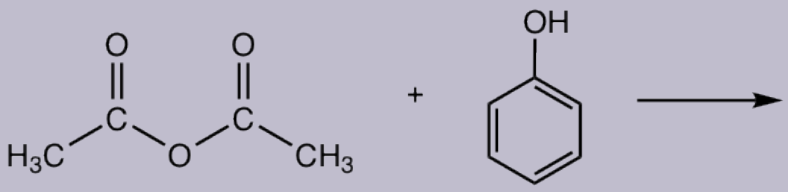
Preparation of Ester from Acyl Chloride or Anhydride

As mentioned earlier both acyl chlorides and anhydrides, the more reactive derivatives, can be employed as starting materials to produce esters (refer to **Fig 7.4b** and **Fig 7.4f**). A few examples are shown below.

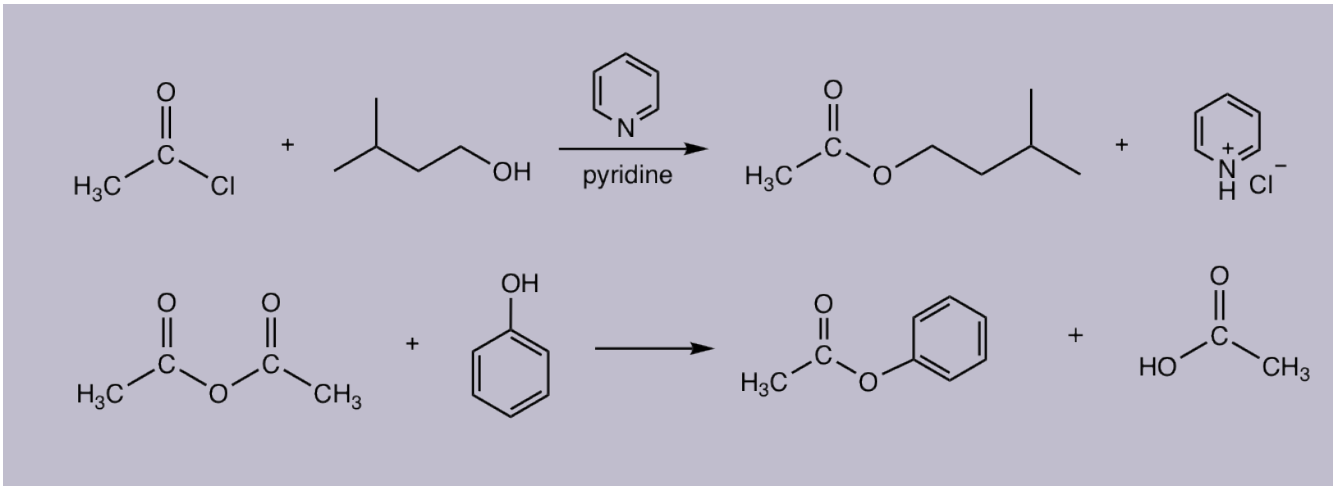
Examples

Show the product of the following reactions.





Answers:



Preparation of Ester by Trans-esterification

An ester reacts with an alcohol R"OH (the R" in alcohol is different from the R' in OR' of the ester) under acidic conditions to form a new ester and a new alcohol. This reaction is called a **trans-esterification** because one ester is converted to another ester. Since the reaction is reversible, strategies that help to shift the equilibrium to the product side should be applied to ensure a high yield of the product, for example, by using an excess of reactant alcohol and removing the product alcohol from the reaction system.

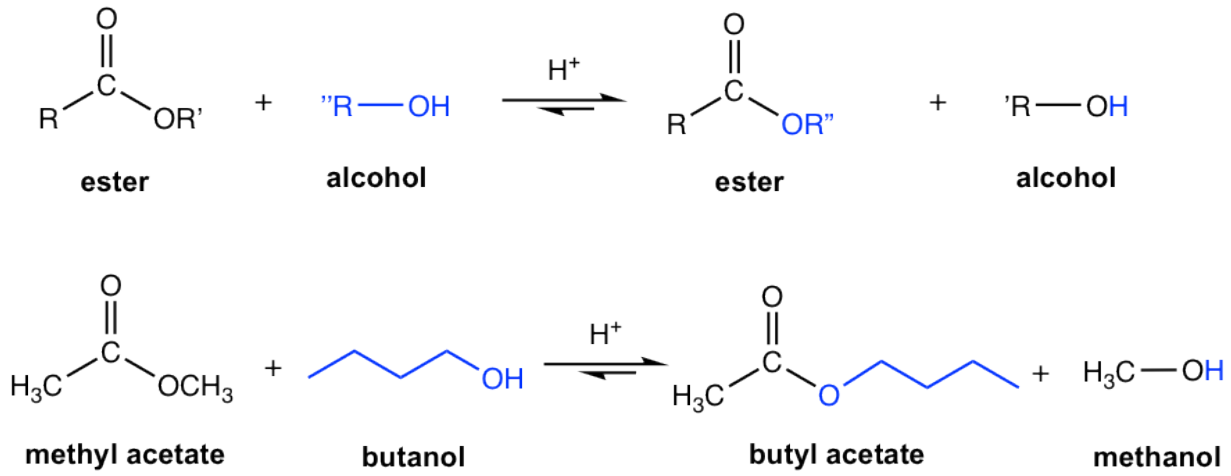


Fig. 7.5c Trans-esterification reaction and an example

The mechanism of the acid-catalyzed trans-esterification is almost the same as the acid-catalyzed esterification of carboxylic acid. Both acid and ester are ***not*** very reactive towards acyl substitution (nucleophilic addition-elimination), protonation with acid helps to increase the electrophilicity of carbon in the carbonyl group and, therefore facilitates the reaction.

7.5.2 Saponification: Base-Promoted Hydrolysis of Ester

Base-promoted hydrolysis of ester is also called **saponification**, which is the chemical reaction that acts as the foundation of soap-making.

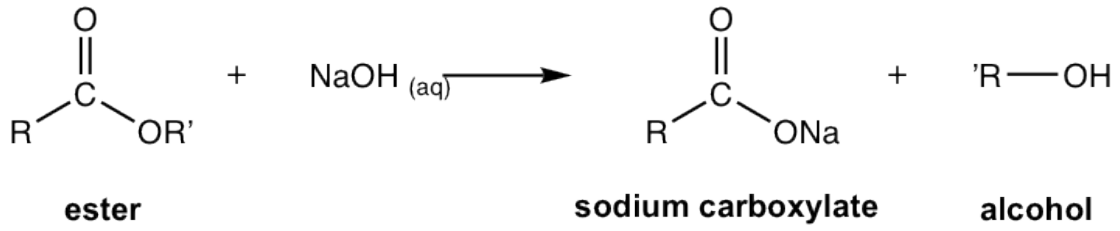


Fig. 7.5d Saponification: base-promoted hydrolysis of ester

The base, OH^-, increases the rate of the hydrolysis of the ester significantly because it is a stronger nucleophile than H_2O, and attacks the carbonyl carbon readily. The product, carboxylate ion, is very unreactive toward nucleophilic substitution because of the negative charge it possesses. The base-promoted hydrolysis reaction, as a result, is irreversible. The mechanism is shown below.

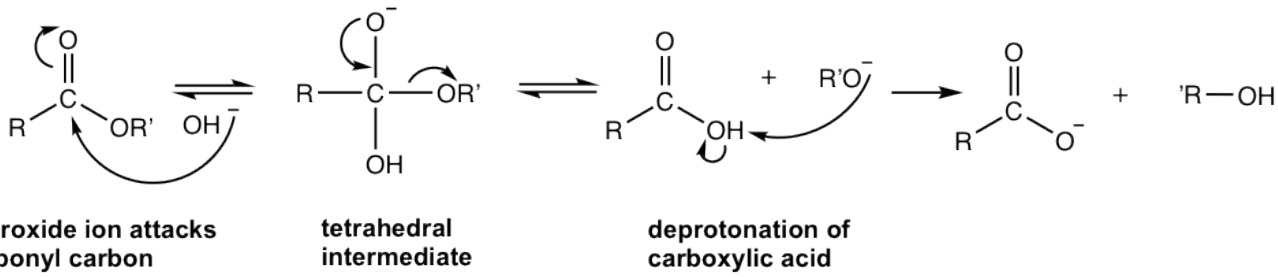


Fig. 7.5e Mechanism for saponification

The chemical structures of soaps are sodium (or potassium) salts of fatty acids. Fatty acids are carboxylic acids with long and unbranched alkyl groups (the length of the R group is usually longer than 16 carbons). Since these acids are obtained from fats, they are called fatty acids. The structures of fats are the triesters of fatty acids with glycerol, the alcohol with three OH groups. Upon base-promoted hydrolysis of the fats (triesters), fats are converted to the sodium (or potassium) salts of fatty acids, which is the soap. The commercial process of soap-making usually involves boiling of fats or oils in sodium hydroxide solutions, and the salt of fatty acid is then precipitated, dried, and pressed into the soap bars.

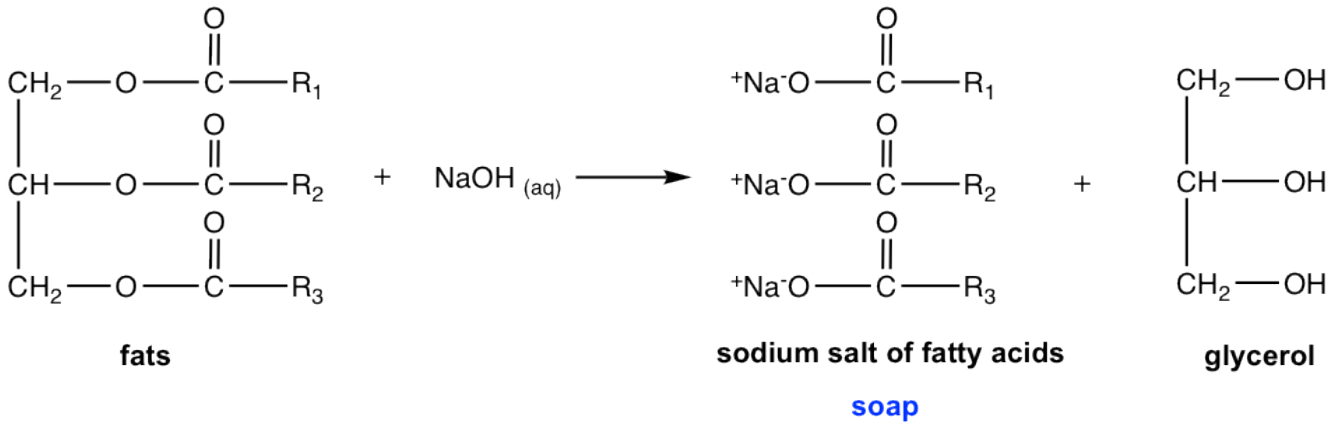


Fig. 7.5f Reaction of soap-making

7.6 Amides

Amide is the least reactive among the group of carboxylic acid derivatives. Being the least reactive one, amide can be prepared by starting from any of the other carboxylic acid derivatives, that is starting with acyl chloride, anhydride, acid, and ester.

Starting from acyl chloride or anhydride, the reaction occurs readily with amines at room temperature to produce amide. The attention is that two equivalents of amines are required to neutralize the side acid product for both reactions (refer to the reaction summary in **Fig 7.4b** and **Fig 7.4f**). Two specific examples are given in Fig. 7.6a.

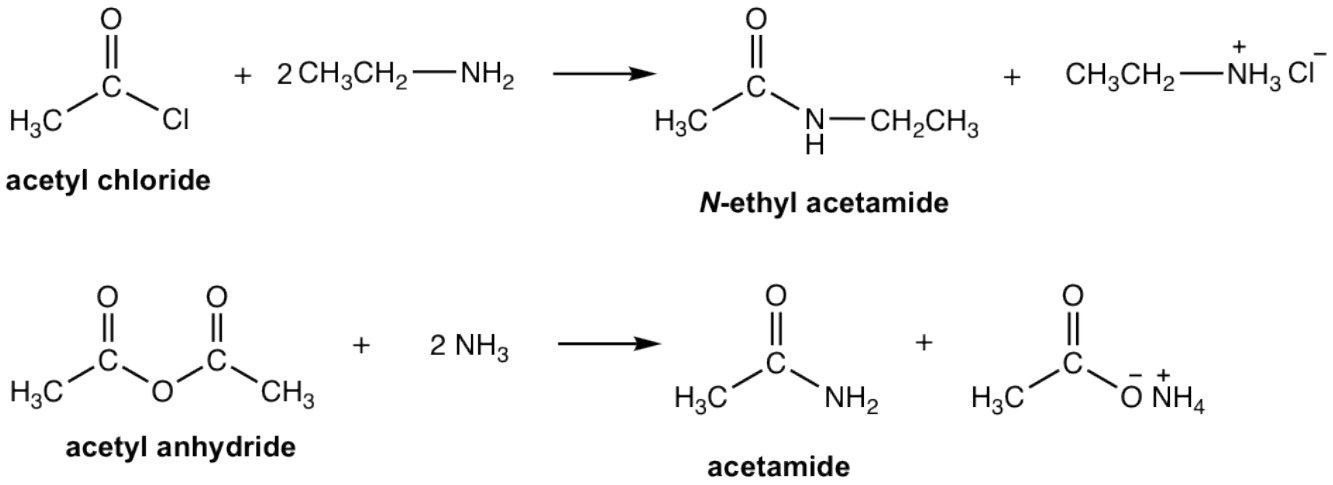


Fig. 7.6a Reactions for preparation of amide from acyl chloride or anhydride

Starting from ester or carboxylic acid, heating is required to prepare amide because of the lower reactivity of these reactants. When acid reacts with amine, an acid-base reaction first occurs to produce the ammonium carboxylate salt, and the salt is converted to amide upon heating.

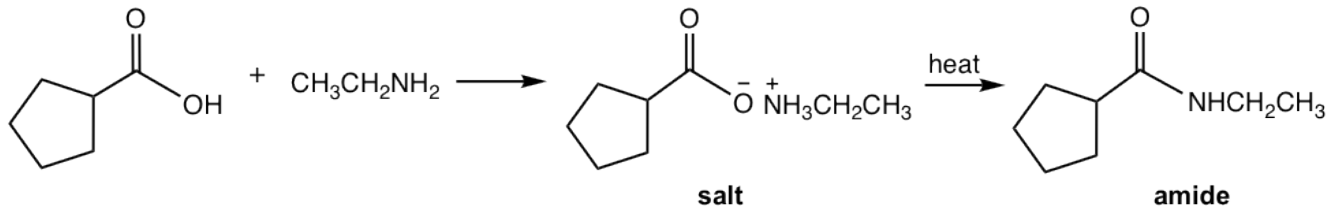
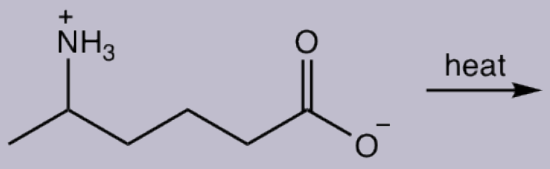


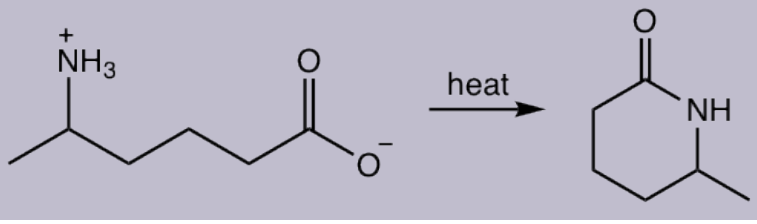
Fig. 7.6b Reaction for preparation of amide from acid

Examples

Show the product obtained when the following compound is heated.



Answer



7.7 Other Reactions of Carboxylic Acid Derivatives

7.7.1 Hydrolysis of Carboxylic Acid Derivatives

The base-promoted hydrolysis of ester represents a specification process of saponification and was discussed in **section 7.5.2**. Actually, all the carboxylic acid derivatives could undergo a hydrolysis reaction, that is reacting with water to produce carboxylic acid and the other components.

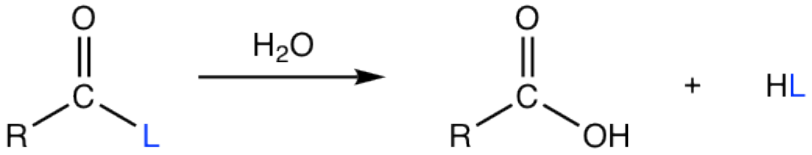


Fig. 7.7a General equation for hydrolysis of carboxylic acid derivatives

The mechanism of the hydrolysis also follows the nucleophilic addition-elimination process generally, therefore the tendency for derivatives to be hydrolyzed also decreases with the order from acyl halide, anhydride, ester to amide. As a result, the reaction condition required for hydrolysis varies for different derivatives, and they are summarized in Table 7.2 below.

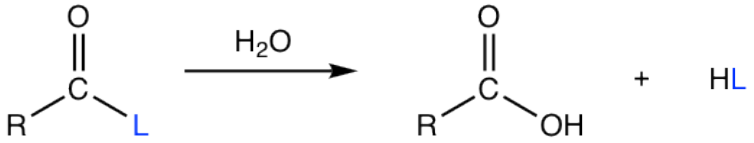
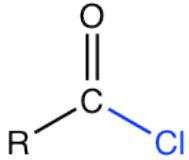
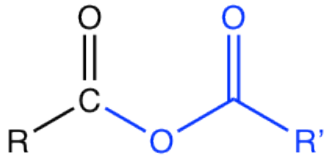
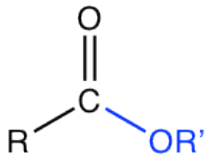
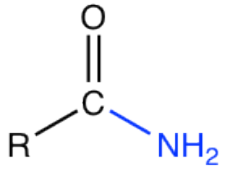
Overall reaction				
Derivatives	 **Acyl halide**	 **Anhydride**	 **Ester**	 **Amide**
Reaction Conditions	Fast reaction at **room temperature, no catalyst** required	**Room temperature, no catalyst** required	Need **catalyst** (H^+ or OH^-) and **heat**	Need **catalyst** (H^+ or OH^-) and **heat**

Table 7.2 Reaction conditions for hydrolysis of carboxylic acid derivatives

Acyl chlorides and anhydrides could be hydrolyzed so easily, that no catalyst was required. For esters and amides, the hydrolysis requires either acid or base as the catalyst, together with heating. Hydrolysis reaction sometimes can be used to prepare certain products, for example, saponification, or hydrolysis of nitrile to produce carboxylic acid. For most cases, however, hydrolysis is something that chemists would need to avoid because it destroys the valuable derivative and converts it back to carboxylic acid. For this reason, some reactive derivatives such as acyl chloride and anhydride are usually stored under specially controlled dry conditions to keep moisture away.

The mechanism for acidic-catalyzed hydrolysis of ester and amide is shown in Fig. 7.7b. You may notice that the mechanism is very similar to the esterification mechanism in Fig. 7.5b. The two mechanisms are reverse processes to each other, and both involve the same steps of **protonation – nucleophilic attack – proton transfer – leaving group leaves – deprotonation**. In hydrolysis, water acts as a nucleophile to attack the protonated carbonyl group, and then HL (ROH for ester or RNH_2 for amide) leaves as a leaving group in the later step.

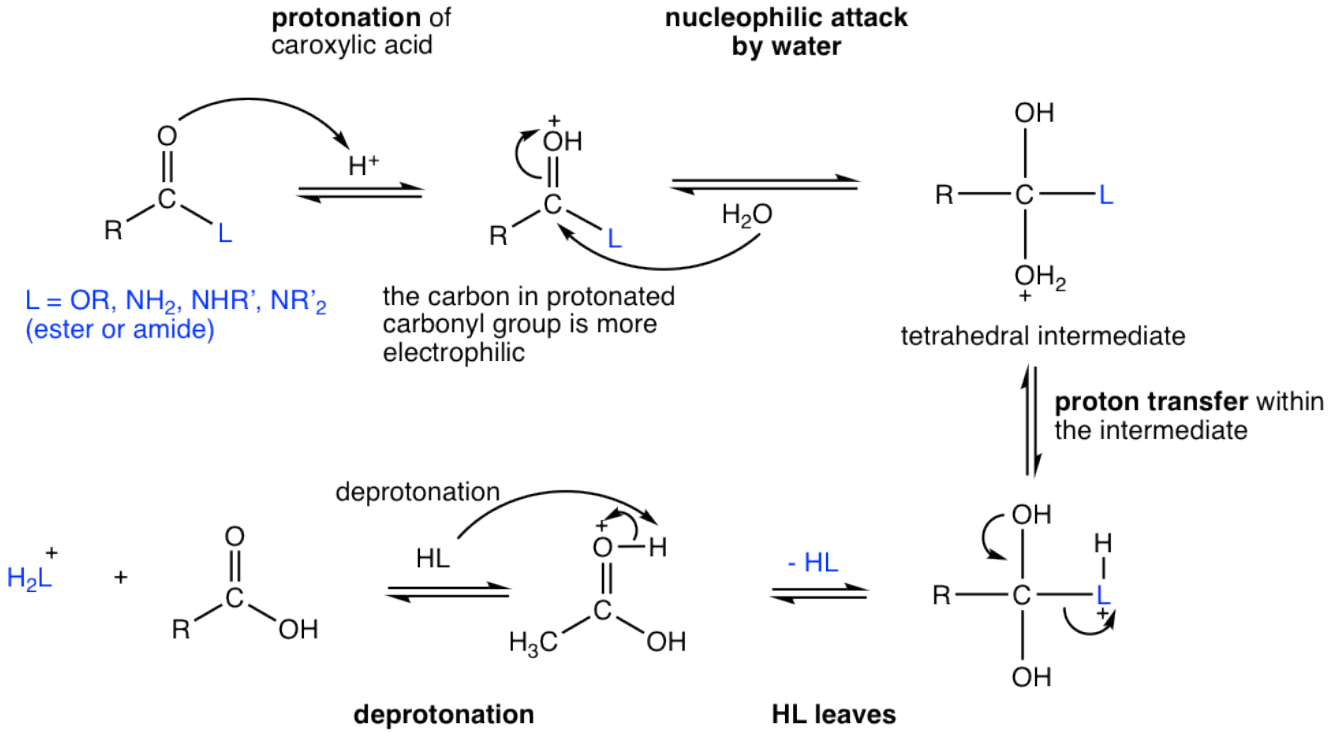
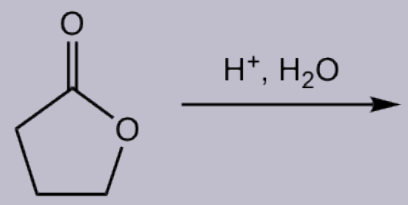

protonation of caroxylic acid
nucleophilic attack by water
L = OR, NH2, NHR', NR'2 (ester or amide)
the carbon in protonated carbonyl group is more electrophilic
tetrahedral intermediate
proton transfer within the intermediate
deprotonation
HL leaves
- HL

Fig. 7.7b General mechanism for acidic hydrolysis of ester or amide

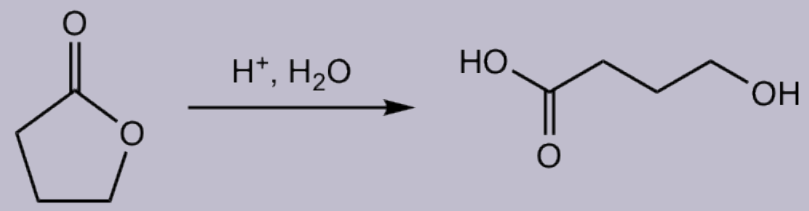
The hydrolysis of ester under basic conditions is also called saponification, as we learned in **section 7.5.2**. The mechanism (shown in Fig. 7.5e) follows the general acyl substitution process involving nucleophilic attack and leaving group leave. The hydrolysis of amide under basic conditions generally follows the same mechanism.

Examples

Show the hydrolysis product:



Answer:



7.7.2 Reaction of Carboxylic Acid Derivatives with Organometallic Reagents

Grignard Reagent

When we learned about the Grignard reaction (**section 1.5.4**), we mentioned that esters react with Grignard reagents. Other derivatives including acyl chloride and anhydride react with Grignard reagent as well. All these derivatives react with two equivalents of Grignard reagent and produce alcohols. The general reaction equation and mechanism are shown here.

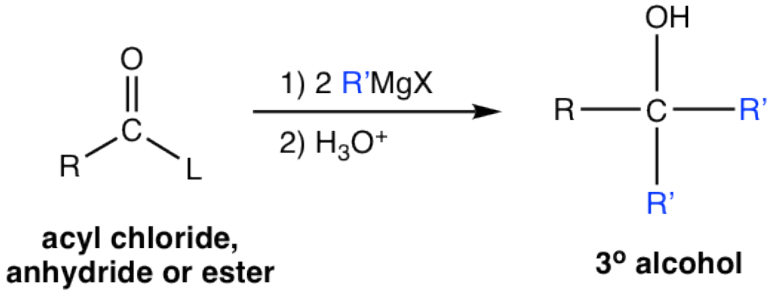


Fig. 7.7c Reaction of acyl chloride, anhydride, and ester with Grignard reagent

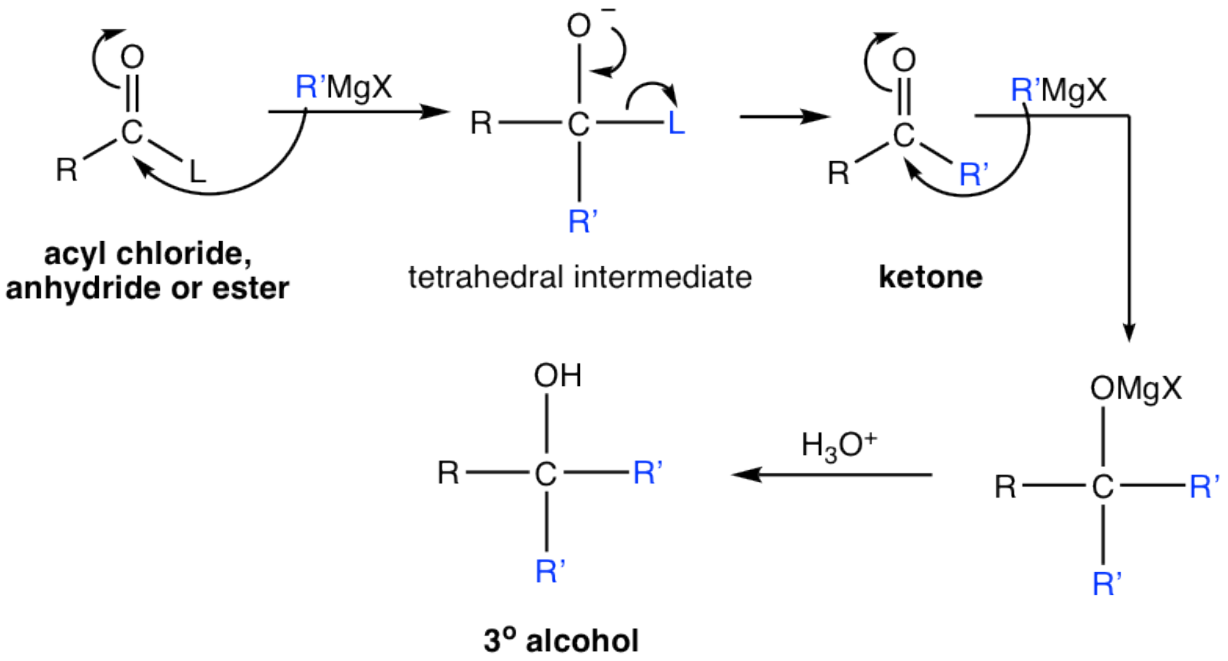


Fig. 7.7d Mechanism for reaction of carboxylic acid derivatives with Grignard reagent

As it is illustrated in the above mechanism the derivative first reacts with one equivalent of R'MgX , by **acyl substitution**, to generate ketone. Then ketone reacts with another equivalent of Grignard reagent R'MgX, by **nucleophilic addition**, and gives the final product — tertiary (3°) alcohol.

Organocuprate Reagent

Organocuprate reagent (refer to **section 6.5.3** for preparation of organocuprate reagent) also reacts with acyl chloride for acyl substitution. Because of the low reactivity of organocuprate, however, it does **not** react with ketone anymore, so ketone is obtained as the final product.

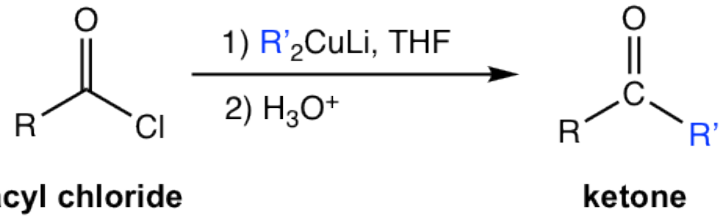


Fig. 7.7e Reaction of acyl chloride with organocuprate reagent

Reducing Agent: $LiAlH_4$ and DIBAL-H

Lithium aluminum hydride, $LiAlH_4$, is a strong reducing agent (refer to **section ??** for structure and property of $LiAlH_4$), and reduces carboxylic acid, acyl chloride, and ester to alcohols (Fig. 7.78f). Please note that two alcohols are obtained for the reduction of ester with $LiAlH_4$. Amides are reduced by $LiAlH_4$ to amines.

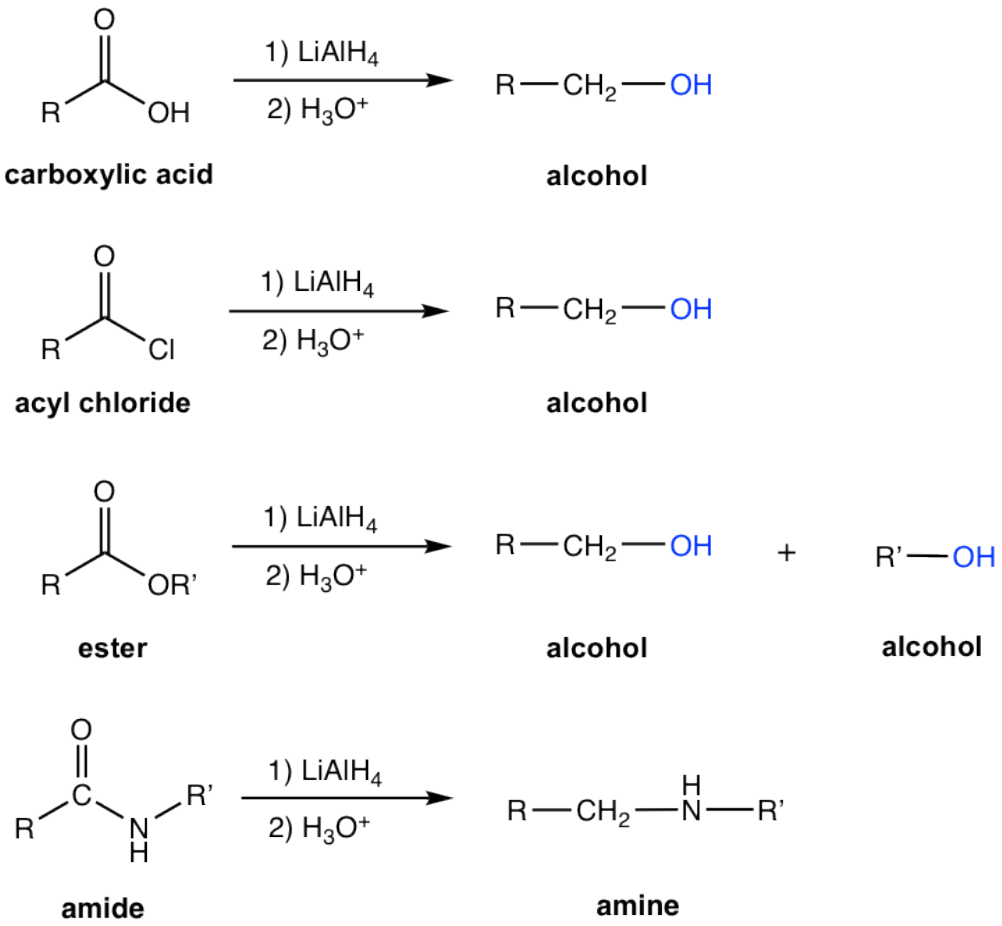
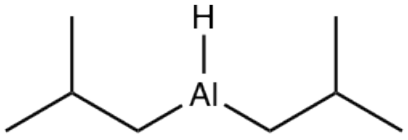


Fig. 7.7f Reduction of carboxylic acid and derivatives by lithium aluminum hydride, $LiAlH_4$

Diisobutylaluminum hydride (DIBAL-H, $(i\text{-}Bu)_2AlH$) is a milder reducing agent than $LiAlH_4$. In the structure of DIBAL-H, two hydrogens in aluminum hydride are replaced by bulky isobutyl groups, and the steric hindrance results in lower reactivity. The reduction of carboxylic acid derivatives with DIBAL-H produces aldehyde as the final product.



diisobutylaluminum hydride (DIBAL-H)

Fig. 7.7g Structure of Diisobutylaluminum hydride

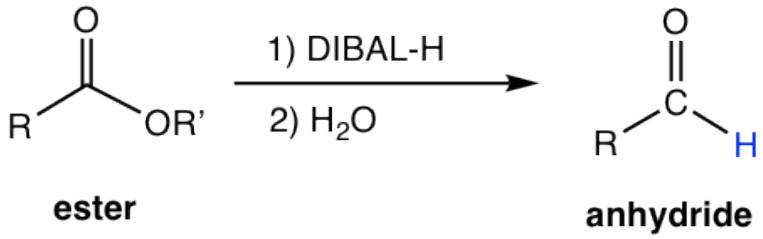


Fig. 7.7h Reduction of the ester by DIBAL-H

7.8 Reactions of Nitriles

7.8.1 Hydrolysis

As mentioned at the beginning of this chapter, nitriles are categorized as carboxylic acid derivatives because they can be converted to carboxylic acid by hydrolysis.

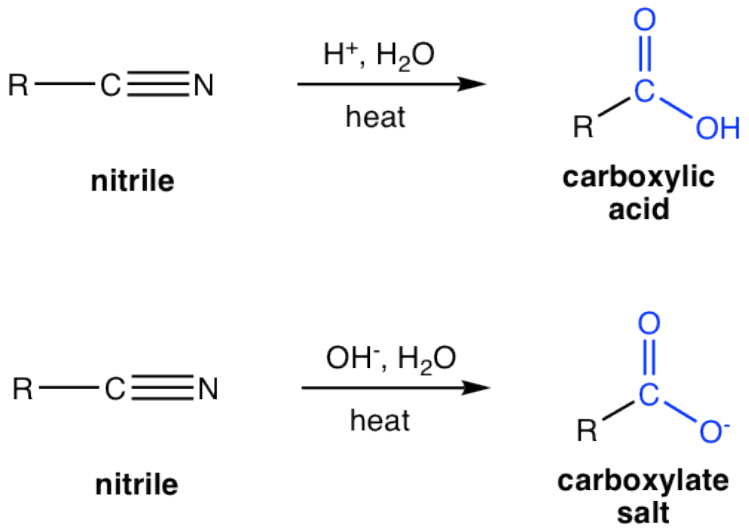


Fig. 7.8a Hydrolysis of nitriles to carboxylic acids

The mechanisms for the hydrolysis of nitrile, in either acidic or basic conditions, are related to the hydrolysis of amide. We will focus on the acidic hydrolysis mechanism (Fig. 7.8b) in this book.

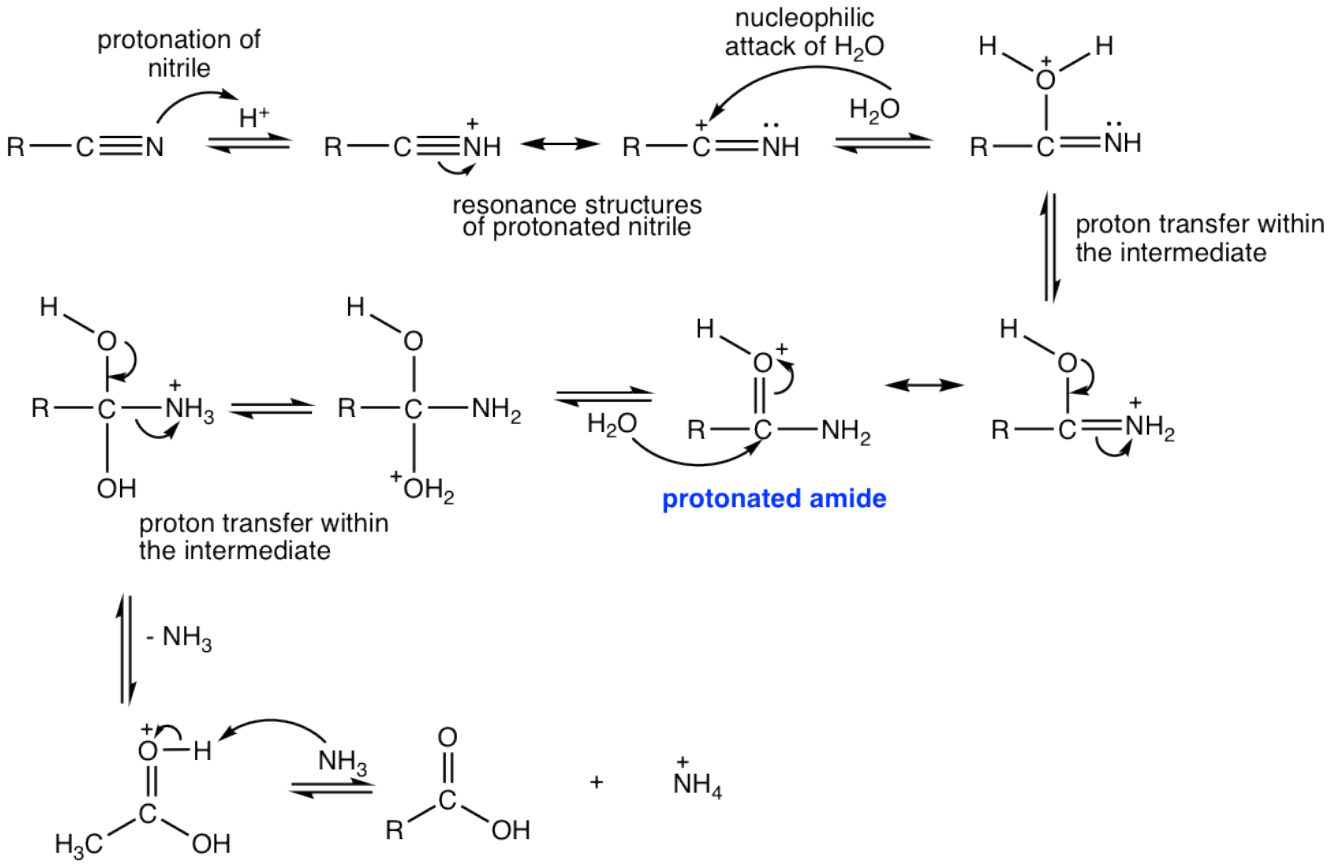


Fig. 7.8b Mechanism for acidic hydrolysis of nitrile

The mechanism for acidic hydrolysis of nitrile involves a couple of key steps as summarized below. Please note that from the step in which **protonated amide** is formed, the following mechanism is just the acidic hydrolysis of amide.

- Protonation of the nitrile group. The protonation increases the polarity of the carbonyl group and makes the carbon atom more susceptible to nucleophilic attack by water, which is a weak nucleophile.
- Nucleophilic attack of water to protonated nitrile.
- Proton is first lost from the oxygen atom and then gained by the nitrogen atom, and the resonance structure after the proton transfer gives a **protonated amide**.
- Acidic hydrolysis of amide to produce carboxylic acid.

7.8.2 Reaction of Nitriles with Organometallic Reagents

The reaction of nitrile with Grignard reagent or organolithium reagent produces ketone as the final product.

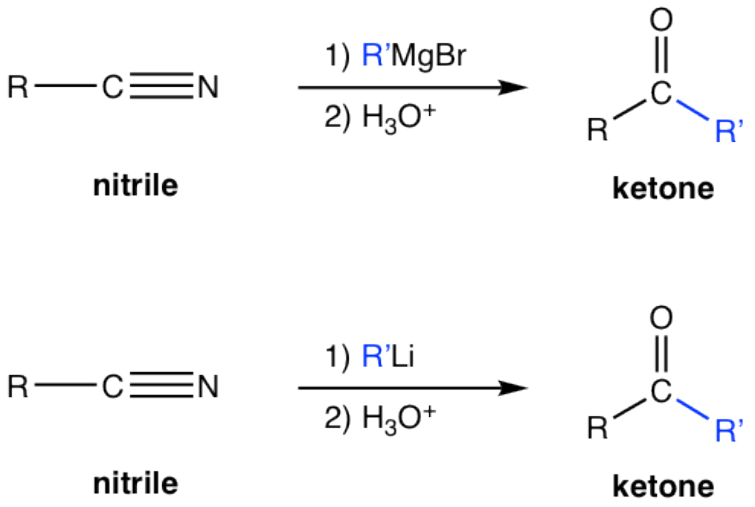


Fig. 7.8c Reaction of nitriles with Grignard reagent or organolithium reagent

7.8.3 Reduction

Reduction of nitrile with milder reducing agent DIBAL-H produces aldehyde.

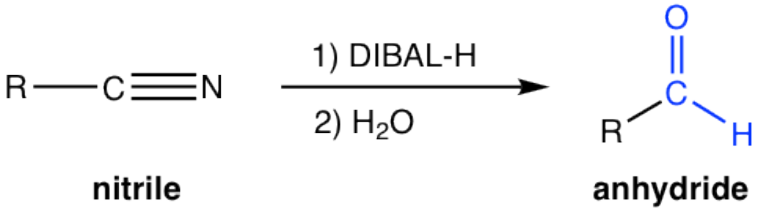
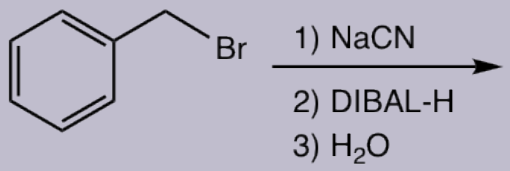


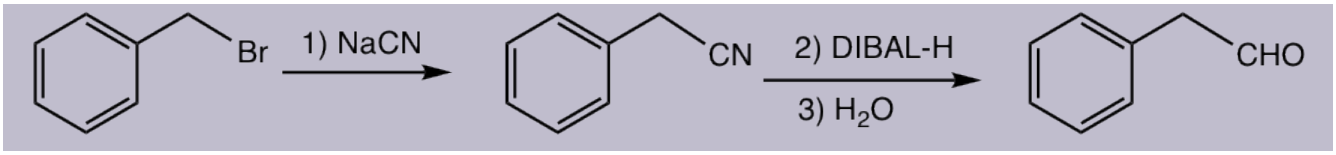
Fig. 7.8d Reduction of nitrile by DIBAL-H

Examples

Show the product of the following reaction.



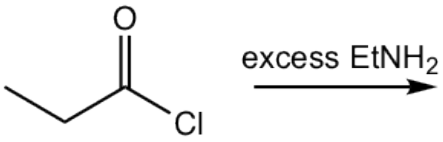
Answer:


Br
1) NaCN
CN
2) DIBAL-H
3) H_2O
CHO

7.9 Practices

1. Show the product of the following reactions.

a.



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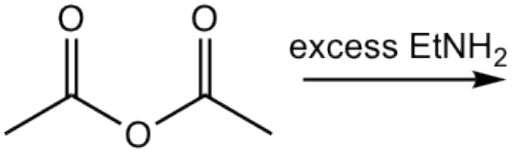

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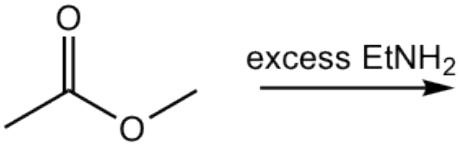

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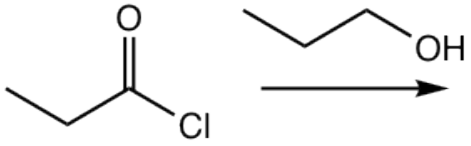

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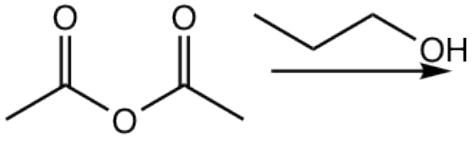

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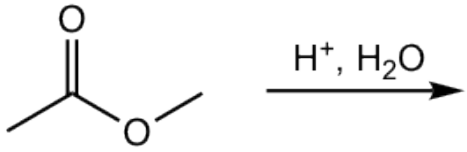
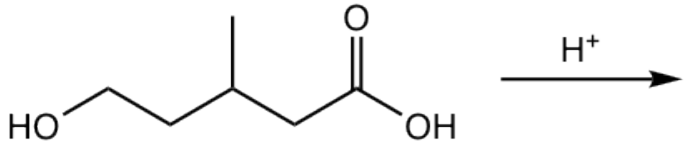


g.



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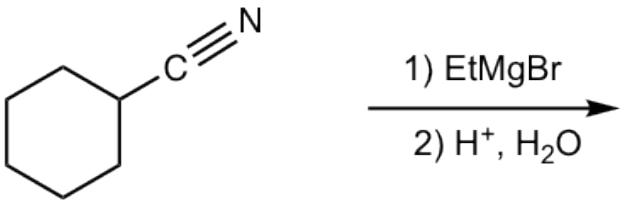
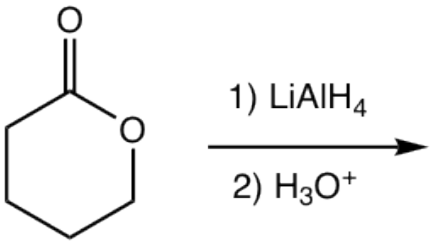


i.



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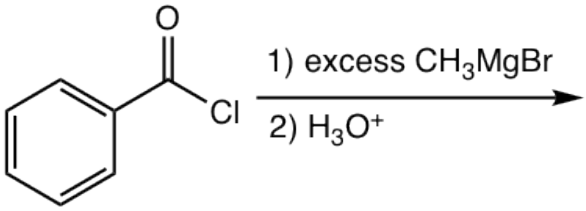
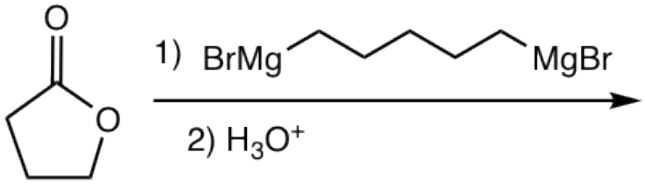
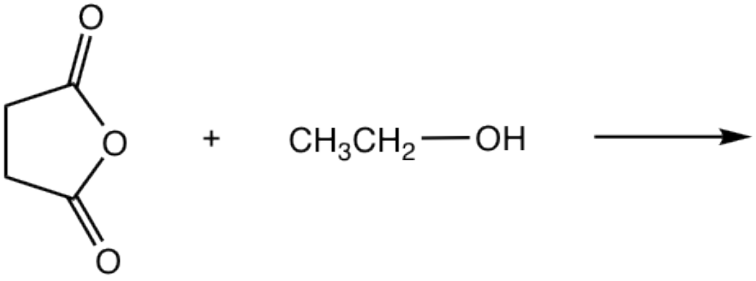


k.



l.

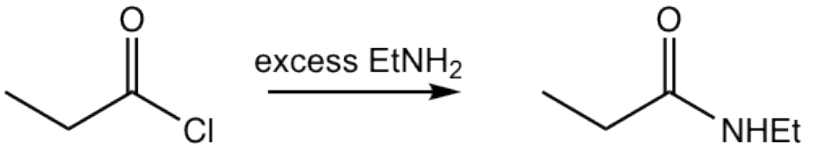


2. Draw the detailed mechanism for the **trans-esterification reaction in Fig. 7.5c** in the book (the conversion of methyl acetate to butyl acetate).

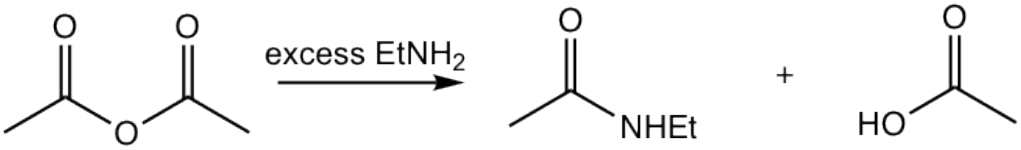
7.10 Practices Answers

1. Show the product of the following reactions.

a.



b.



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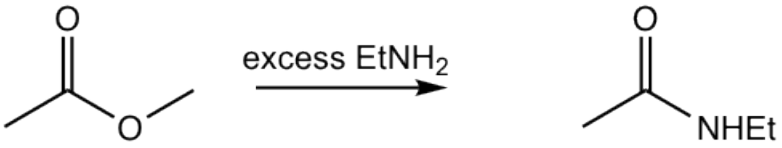

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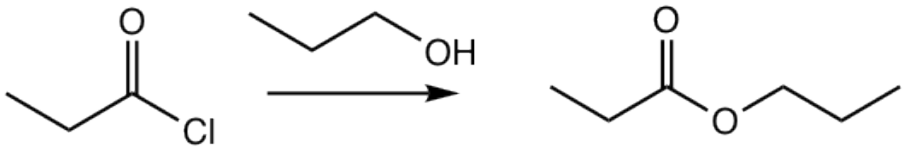
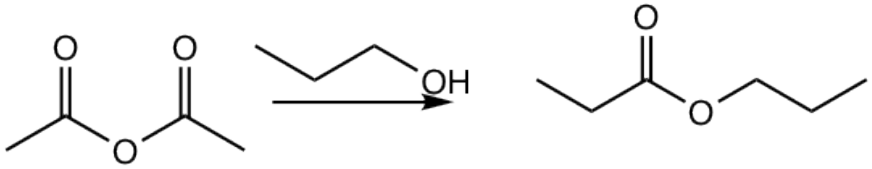


e.



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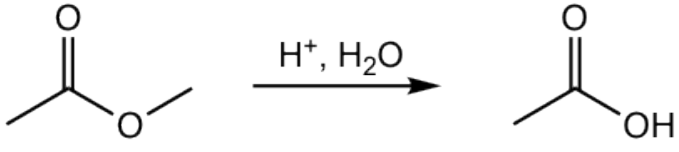

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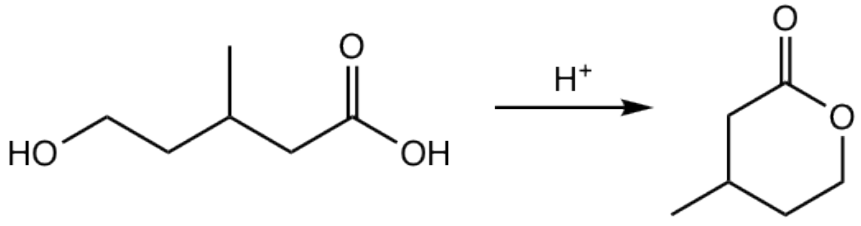

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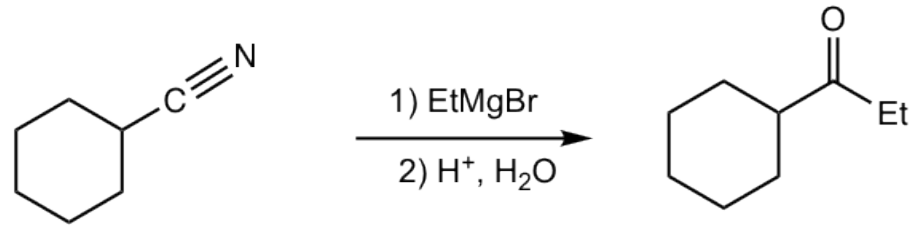
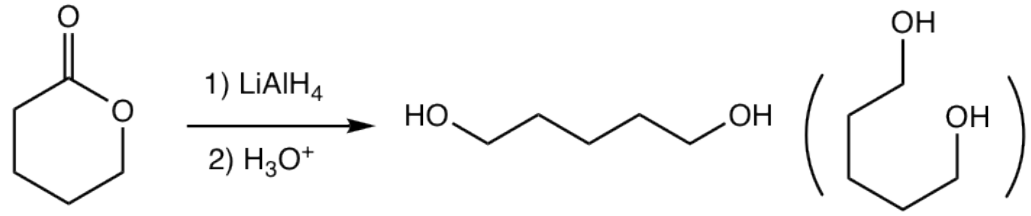


i.



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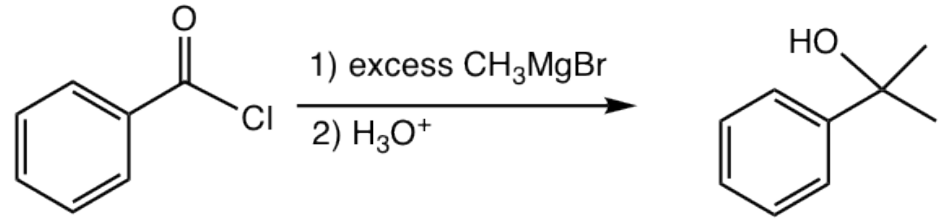

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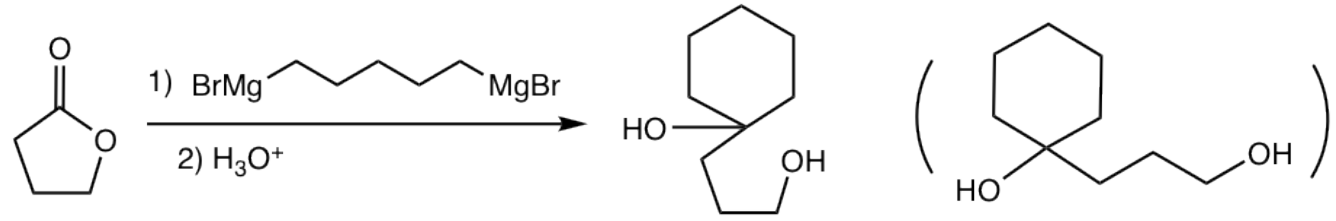

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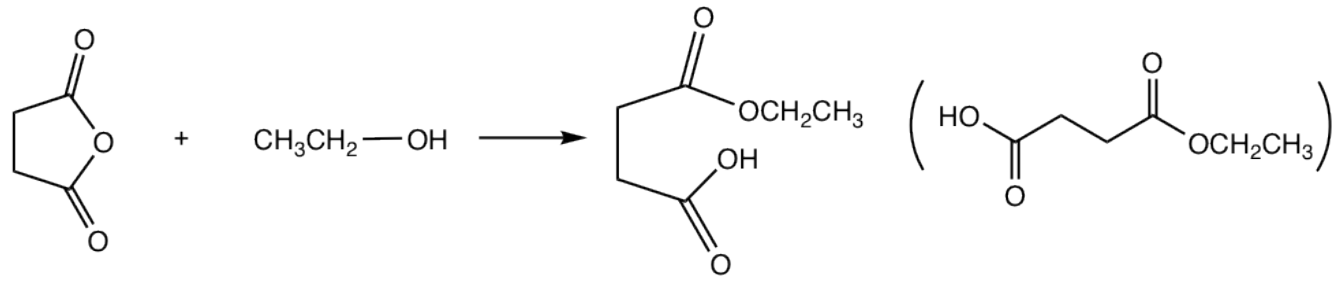
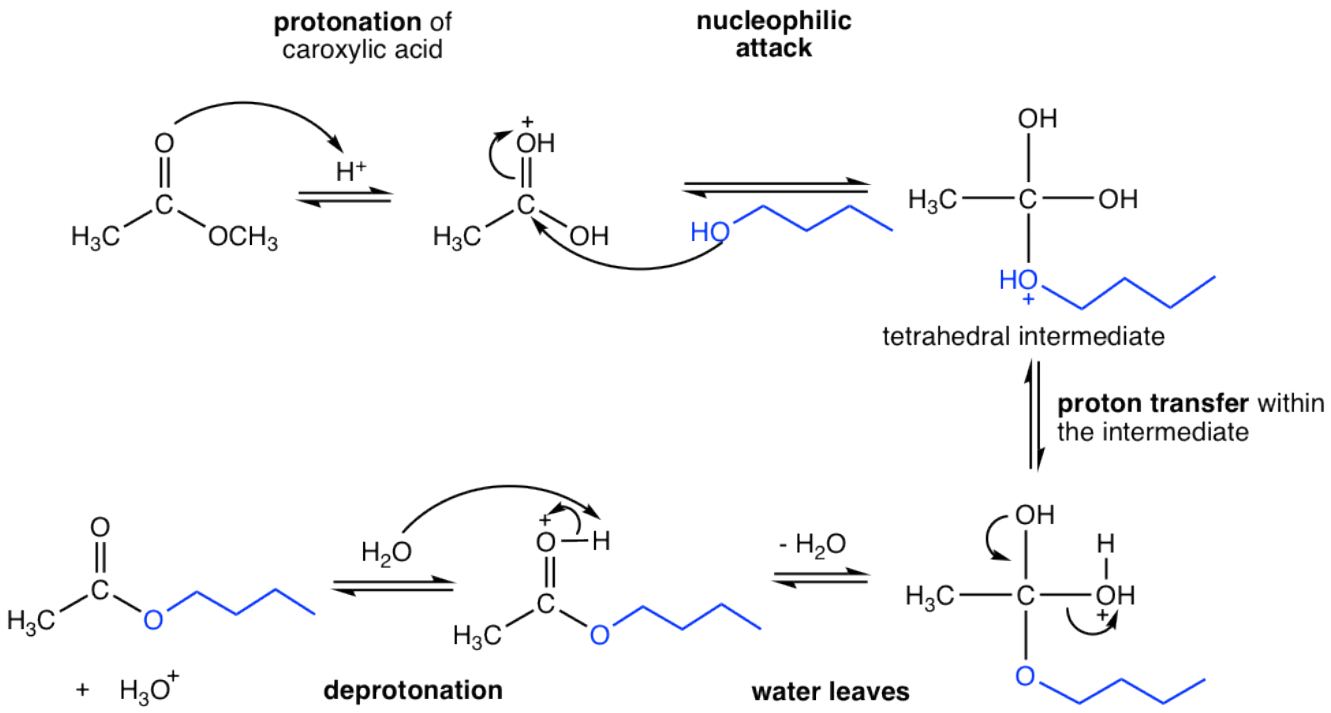


2. Draw the detailed mechanism for the **trans-esterification reaction in Fig. 7.5c** in the book (the conversion of methyl acetate to butyl acetate).


protonation of caroxylic acid
nucleophilic attack
tetrahedral intermediate
proton transfer within the intermediate
deprotonation
water leaves

CHAPTER 8: THE CLAISEN CONDENSATION AND APPLICATIONS IN SYNTHESIS

In Chapter 6, we discussed aldol reaction/condensation, the reaction between the enolate of aldehydes or ketones with the carbonyl group of aldehydes or ketones. The α hydrogens in carboxylic esters are also rather acidic, with pK_a in the range of about 25. Here we will explore the reaction of ester enolate, specifically the condensation of ester enolate with the carbonyl group in ester, which is called the **Claisen Condensation.**

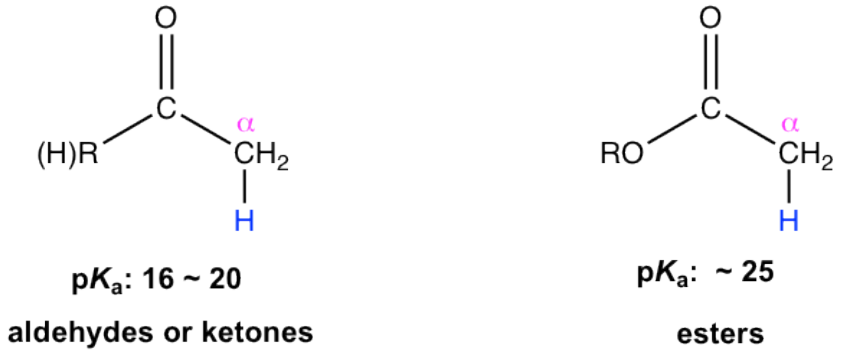


Fig. 8.1 pK_a of aldehydes/ketones and esters

8.1 Claisen Condensation Fundamentals

The general reaction equation of Claisen condensation is shown in Fig. 8.1a. Please note that the overall reaction condition involves an acidic work-up process, the reason for this will be explained in the mechanism. In a Claisen Condensation, the enolate of one ester molecule (black one) acts as the nucleophile to do acyl substitution (nucleophilic addition-elimination) to another ester molecule (blue one). A new C-C bond (red bond) connects the two units together and β-keto ester is the product produced. In Chapter 6 we saw how β-keto esters are useful in synthesis, therefore Claisen condensation is a reaction that has important and broad applications in synthesis.

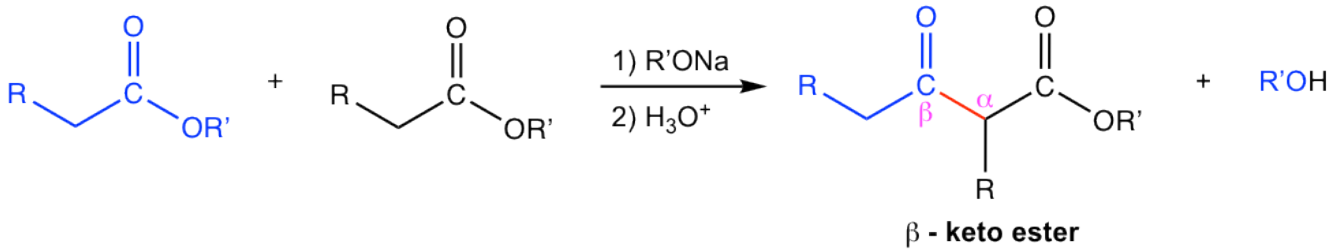


Fig. 8.1a General reaction equation of Claisen condensation

The detailed reaction mechanism is shown in Fig. 8.1b.

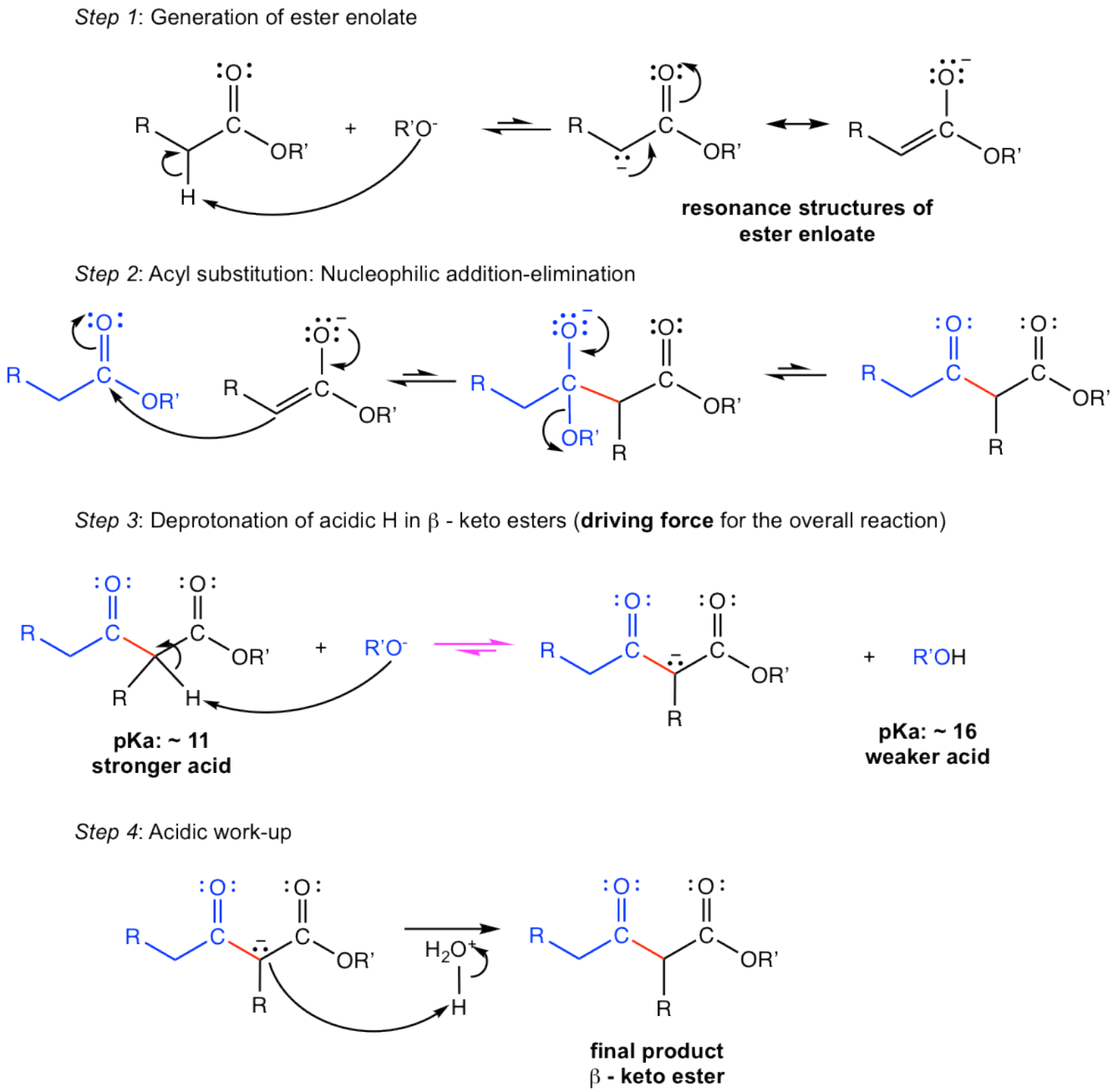

Step 1: Generation of ester enolate
resonance structures of ester enloate
Step 2: Acyl substitution: Nucleophilic addition-elimination
Step 3: Deprotonation of acidic H in β - keto esters (driving force for the overall reaction)
pKa: ~ 11
stronger acid
pKa: ~ 16
weaker acid
Step 4: Acidic work-up
final product
β - keto ester

Fig. 8.1b General reaction mechanism of Claisen condensation

Further explanations of the mechanism:

- The enolate of one ester molecule is generated in the first step, and then acts as the nucleophile to attack the carbonyl group of another ester molecule. The 2nd ester molecule undergoes the acyl substitution by getting rid of the $R'O^-$, and produces the β-keto ester in step 2.
- **Special attention**: both equilibria in steps 1 and 2 are ***unfavorable towards the product***. In step 1: the α-hydrogen in ester is a weaker acid than an alcohol. In step 2, the $R'O^-$ group is a poor leaving group. To draw the overall equilibrium towards the product side, another deprotonation step (step 3) of the β-keto esters is necessary.

- The α-hydrogen in β-keto esters is more acidic (with pKa of about 11) than alcohol (pKa is about 16), therefore $R'O^-$ is a base that is strong enough to deprotonate the α-hydrogen in β-keto esters. As a result, step 3 is highly favorable and draws the overall equilibrium towards the product side. **The Claisen condensation reaction will not be productive without this critical step**. The neutral final product is formed by the acidic work-up step in step 4.
- Ester that has only one α-hydrogen therefore does **not** undergo Claisen condensation, because it does not have acidic α-hydrogen to be deprotonated in step 3 of the mechanism.

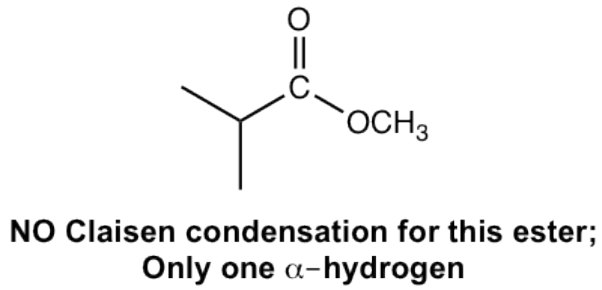


Fig. 8.1c Example of ester that does not undergo Claisen condensation

- Alkoxide is usually used as the base in Claisen condensation. The alkyl group in alkoxide should be the **same** as the alkoxyl group of the ester, both shown as R'O in the above general equation and mechanism. Hydroxide (OH^-) cannot be used as a base for Claisen condensation because it could react with the ester for hydrolysis.

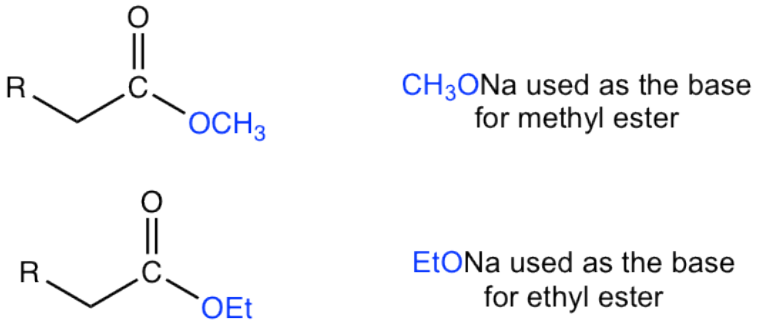


Fig. 8.1d The proper base used in Claisen condensation

8.2 Other types of Claisen Condensation

8.2.1 Intramolecular Claisen Condensation: the Dieckmann Condensation

For a molecule that contains two ester groups, an intramolecular version of the Claisen condensation could occur, which is called the **Dieckmann Condensation**. Dieckmann condensation is favorable when a 5- or 6-membered ring is formed. An example is given below.

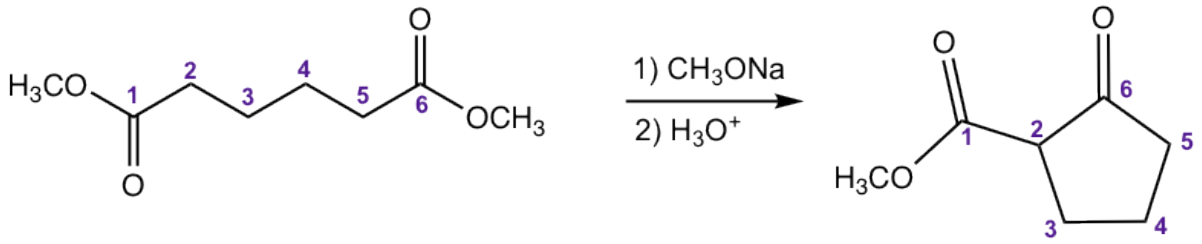


Fig. 8.2a Dieckmann condensation example

8.2.2 Crossed Claisen Condensation

Crosse Claisen condensation is the reaction between two different molecules.

Crossed Claisen Condensation between two Different Esters

For the two esters, one ester has **no** α-hydrogen and the other ester has α-hydrogens. The ester with α-hydrogen becomes enolate in the presence of bases, and the enolate reacts with the carbonyl group in the other ester. As shown in the following example (Fig. 8.2b) that methyl benzoate is the ester has **no** α-hydrogen, it undergoes crossed Claisen condensation with the methyl acetate that has α-hydrogens.

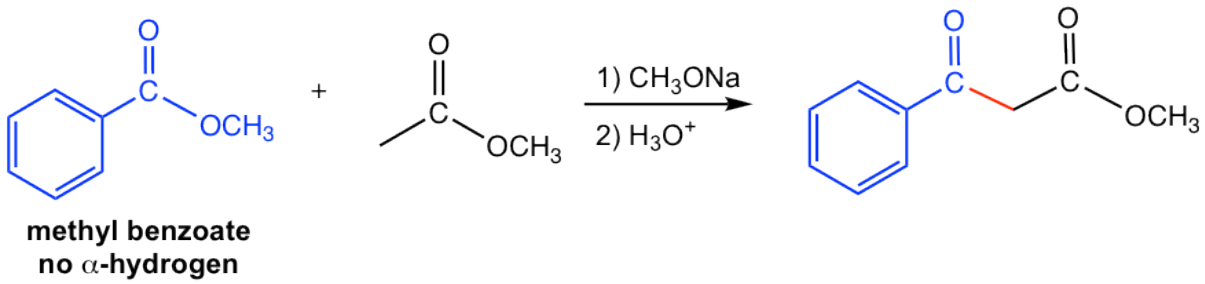


Fig. 8.2b Crossed Claisen condensation example

The other esters that have no α-hydrogen include formate, carbonate and oxalate, as the examples given in Fig. 8.2c.

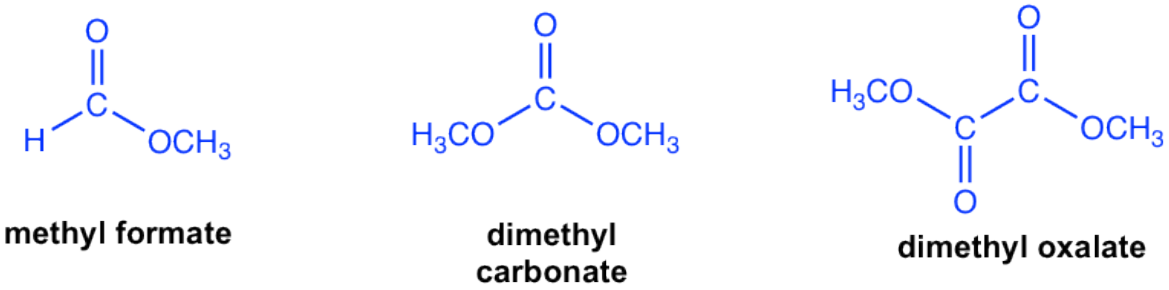
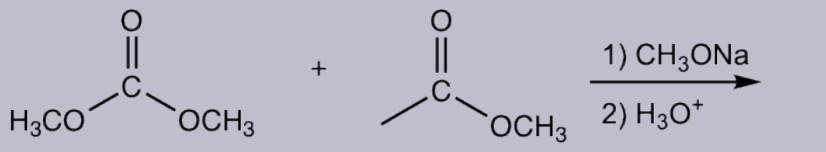
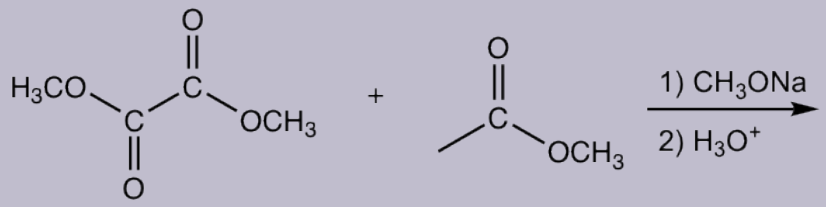


Fig. 8.2c Examples of ester has no α-hydrogen

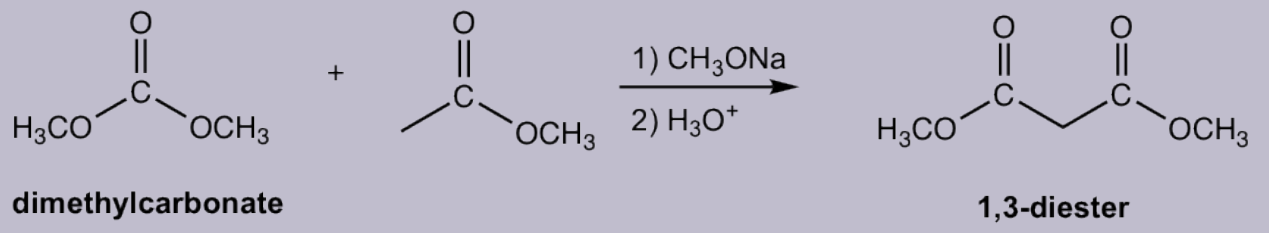
Examples

Show the product of the following reactions.



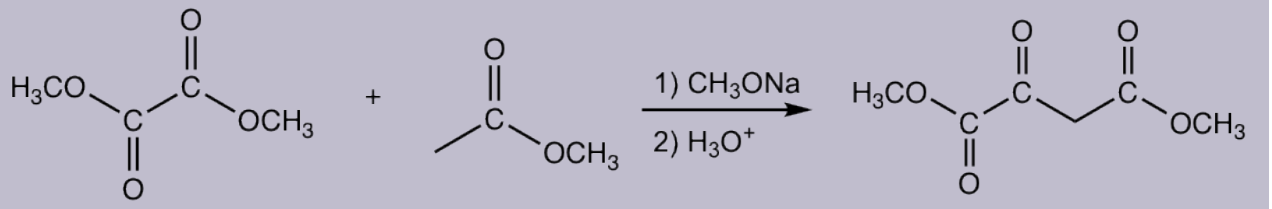


Answers:



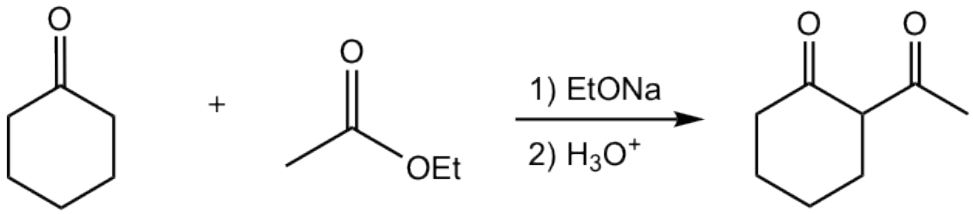
dimethylcarbonate **1,3-diester**

Note: 1,3-diester is formed for condensation with carbonate.



Crossed Claisen Condensation between Ester and Ketone

The other type of crossed Claisen condensation is between one ketone and one ester. The α-hydrogen of the ketone is more acidic than that in ester, therefore the ketone enolate is formed preferably and reacts with ester in acyl substitution. As shown in the following example 1,3-diketone is usually the product for such reaction.

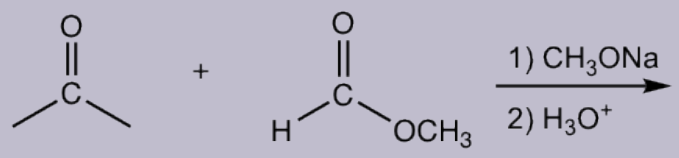


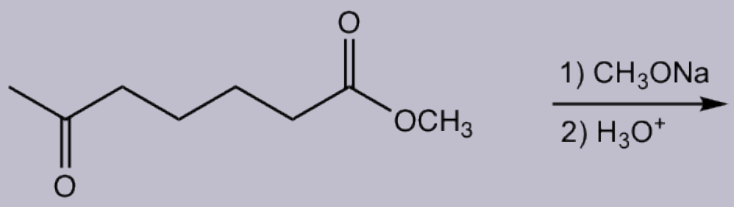
ketone **ester** **1,3-diketone**

Fig. 8.2d Crossed Claisen condensation between ketone and ester

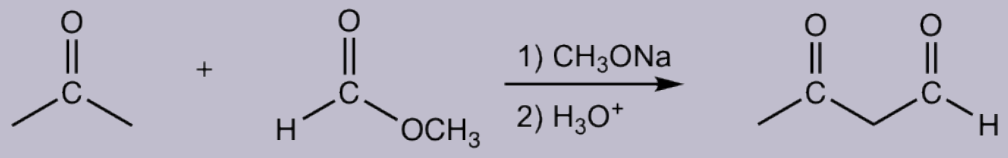
Examples

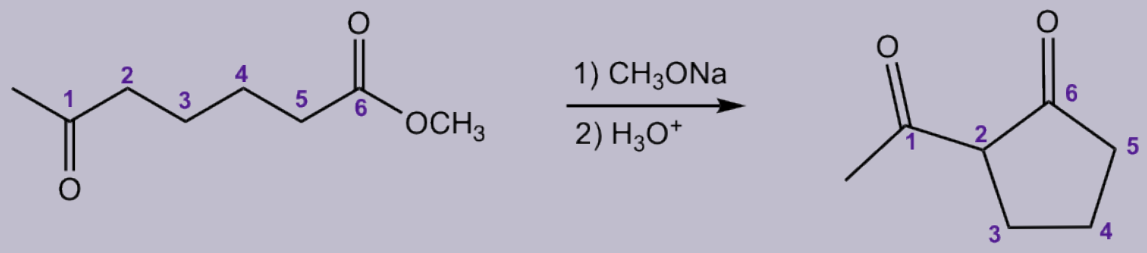
Show the product.





Answers:





8.3 β-dicarbonyl Compounds in Organic Synthesis

Depending on the structures of the reactant, different products could be generated in Claisen condensation, for example, β-keto ester, 1,3-diester, or 1,3-diketone, and they could all be generally categorized as **β-dicarbonyl compounds**. As mentioned in the earlier section the α-hydrogens in β-dicarbonyl compounds show great acidity (**section 6.5.4,** and in Fig. 8.3a), and therefore β-dicarbonyl compounds are important compounds that have unique applications in organic synthesis.

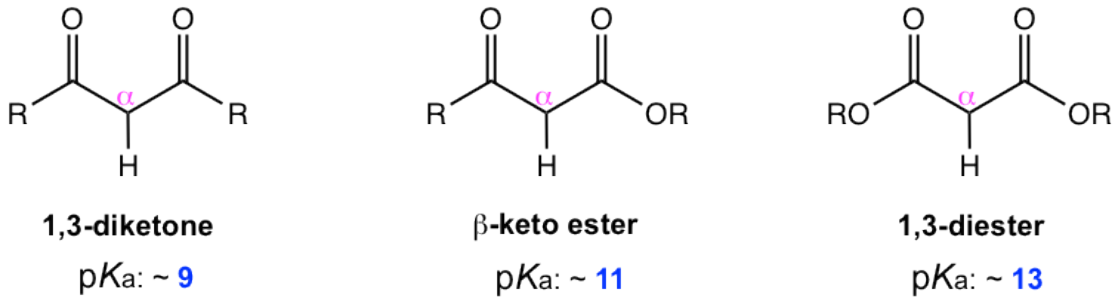


Fig. 8.3a pKa range of α-hydrogens in β-dicarbonyl compounds

8.3.1 Alkylation of β-dicarbonyl compounds

An enolate can be easily generated by treating a β-dicarbonyl compound with base, for example, alkoxide RO^-. The resulting enolate, which is a nucleophile, undergoes alkylation with alkyl halide in an S_N2 reaction. This reaction proceeds in the same way as the alkylation of other enolates (**section 6.3**).

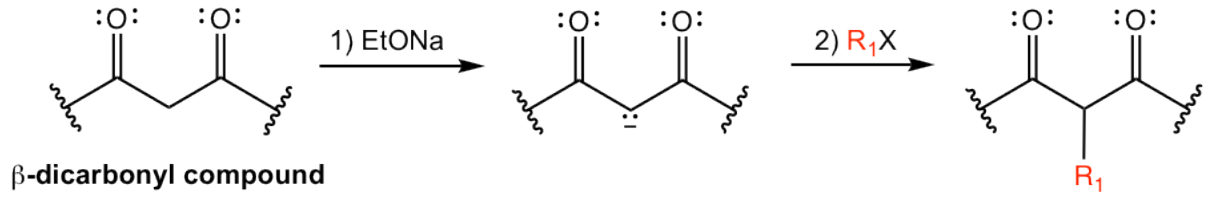


Fig 8.3b Alkylation of β-dicarbonyl compounds

After the first alkyl group is introduced, there is still one acidic hydrogen available in the β-dicarbonyl compound, and if we desire, a second alkylation can be carried out. Two different alkyl groups can be introduced into the structure with two separate alkylation steps.

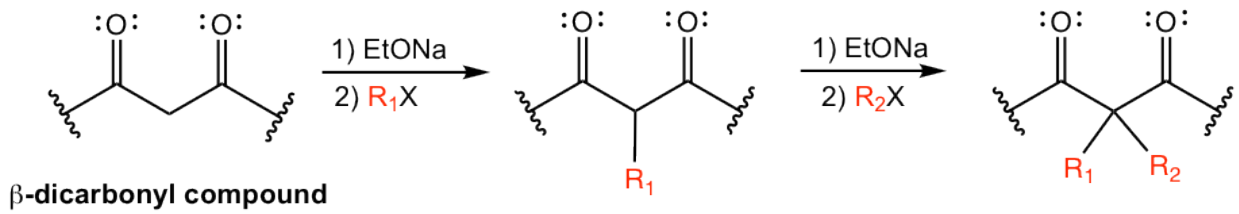


Fig 8.3c Dilkylation of β-dicarbonyl compounds

8.3.2 Decarboxylation of β-keto carboxylic acid

Decarboxylation is the reaction whereby a carboxylic acid loses a CO_2 molecule. For most carboxylic acids, decarboxylation is difficult to be carried out. For β-keto carboxylic acid, that is the carboxylic acid with a carbonyl group one carbon away from the COOH group, decarboxylation occurs readily with heating.

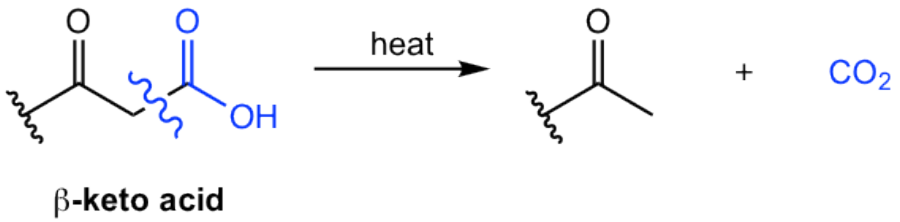


Fig 8.3d Decarboxylation of β-keto carboxylic acid

The reason for the ease of decarboxylation is that the carbonyl group at the β-position helps to form a six-membered cyclic transition state (Fig. 8.3e), that leads to the removal of the CO_2 molecule and generation of an enol. The enol then tautomerizes to a ketone.

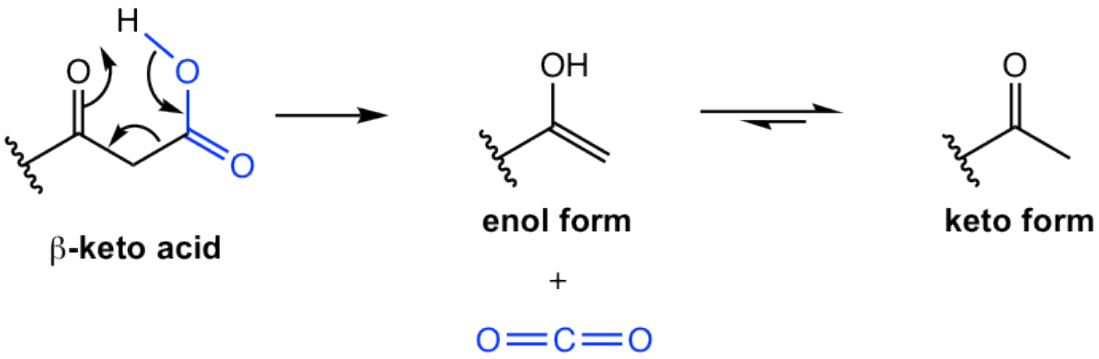


Fig 8.3e Mechanism for decarboxylation of β-keto carboxylic acid

8.3.3 Application of Two Specific β-dicarbonyl Compounds in Synthesis

In organic synthesis, alkylation and decarboxylation are usually applied as subsequent steps to β-dicarbonyl compounds, to synthesize target products with specific structures. We will focus on the applications of two specific β-dicarbonyl compounds in this section, each represents a way for synthesizing one specific type of structure.

Acetoacetic Ester in Synthesis

One specific compound that has a very common application in synthesis is **ethyl acetoacetate**. Ethyl acetoacetate can be prepared by self-Claisen condensation of ethyl acetate.

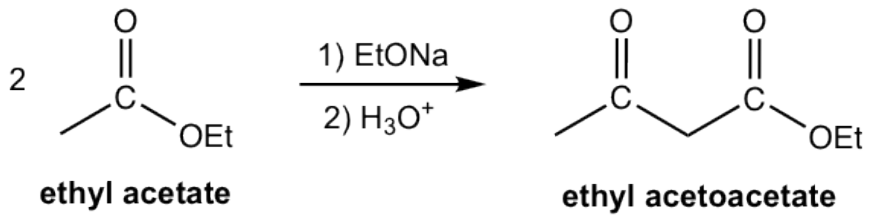


Fig 8.3f Preparation of ethyl acetoacetate

Upon alkylation, followed by hydrolysis and decarboxylation, ***ethyl acetoacetate is a useful reactant for the preparation of substituted methyl ketones*** (Fig 8.3g). Based on the structure of the target methyl ketone, i.e., the specific structure of R_1 and R_2, the corresponding alkyl halide can be employed either once or twice. The alkylated ethyl acetoacetate then be hydrolyzed to the alkylated acetoacetic acid, which undergoes decarboxylation with heating to produce the desired substituted methyl ketones.

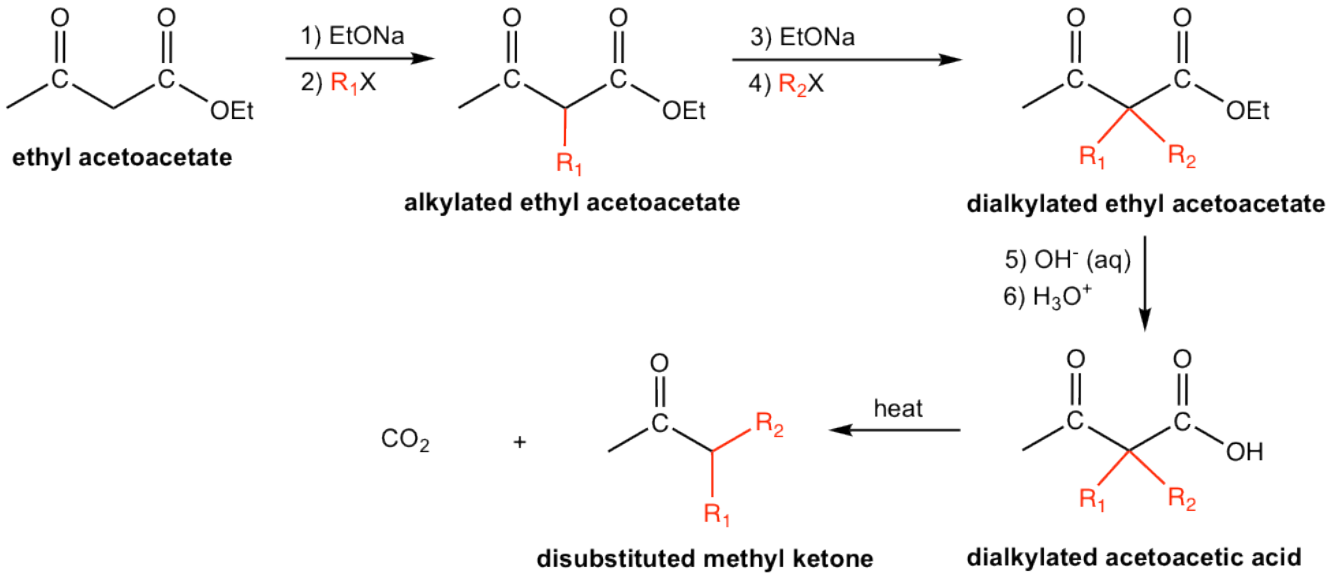
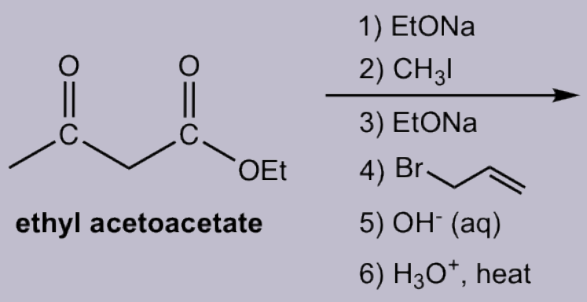


Fig 8.3g General Synthesis Route of Substituted Methyl Ketone from Ethyl Acetoacetate

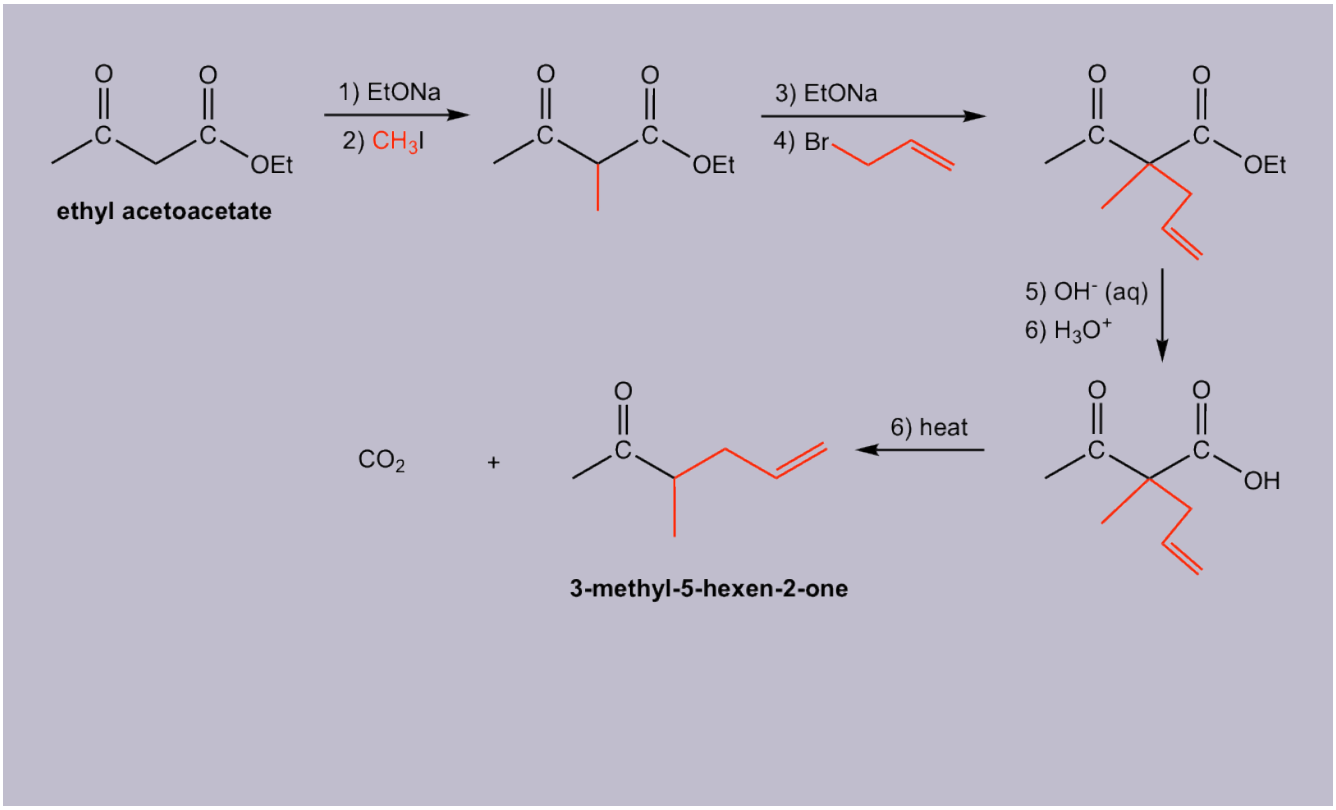
Examples

Show products of the following multi-step reaction.



Answers:

All the steps can be put together on the reaction arrows. Only the final product is required for this question, the products for the middle steps are shown for study purposes.



Malonic Ester in Synthesis

Another group of b-dicarbonyl compounds that has broad application in synthesis is the ester of malonic acid, with the specific example as **diethyl malonate** (or dimethyl malonate, which can be used in almost exactly the same way).

Diethyl malonate is prepared from the cross-Claisen condensation between diethyl carbonate and ethyl acetate.

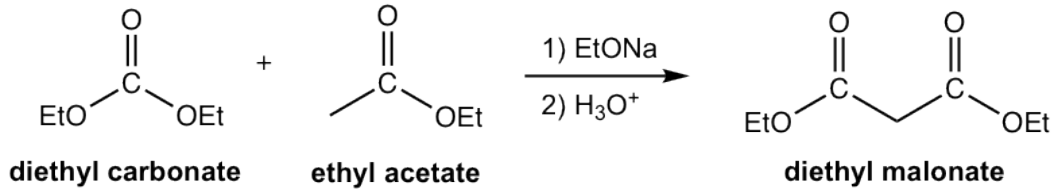


Fig. 8.3h Preparation of diethyl malonate

Applying the same synthesis strategy of alkylation, hydrolysis and decarboxylation, ***diethyl malonate is a useful reactant for the preparation of substituted carboxylic acid***, as shown in the general equation here.

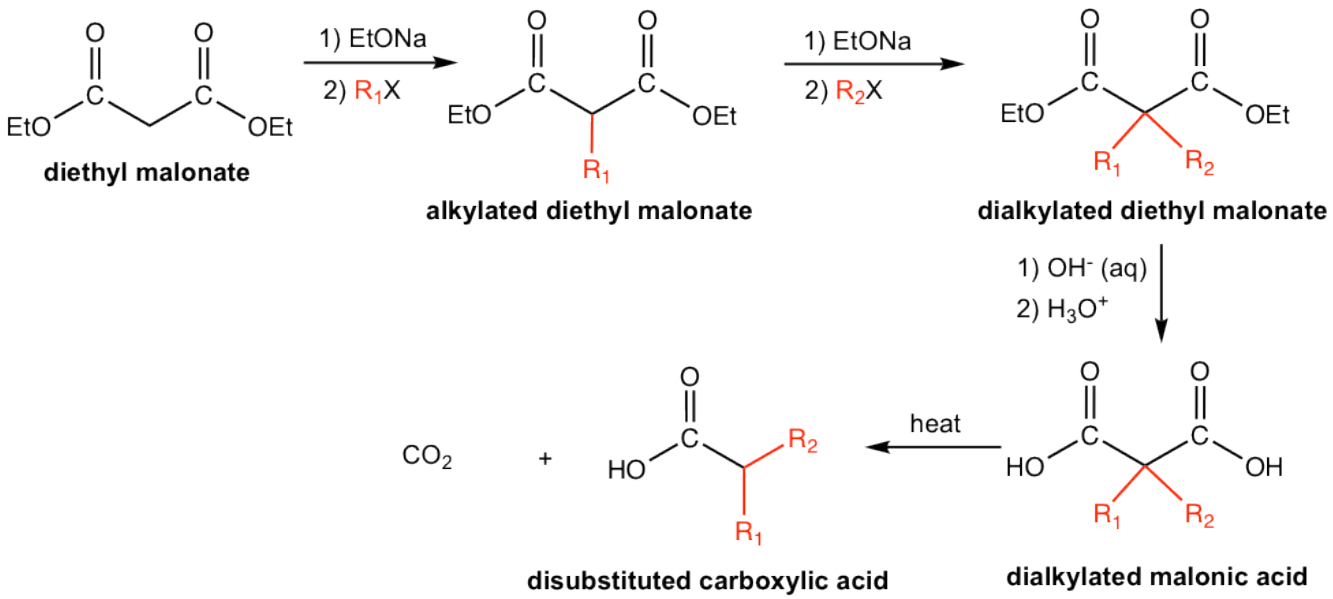
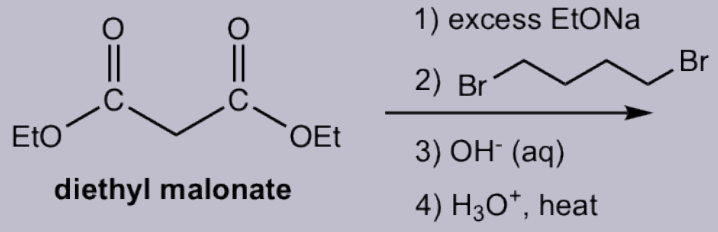


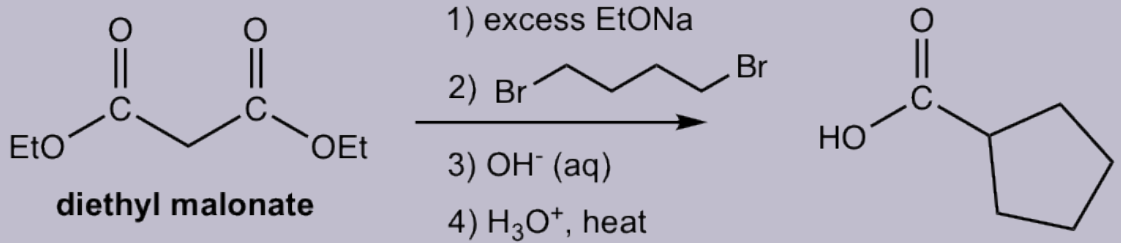
Fig 8.3i General Synthesis Route of Substituted carboxylic acid from diethyl malonate

Examples

Show the product.



Answer:



The synthesis applications of ethyl acetoacetate and diethyl malonate are summarized in Fig. 8.3j.

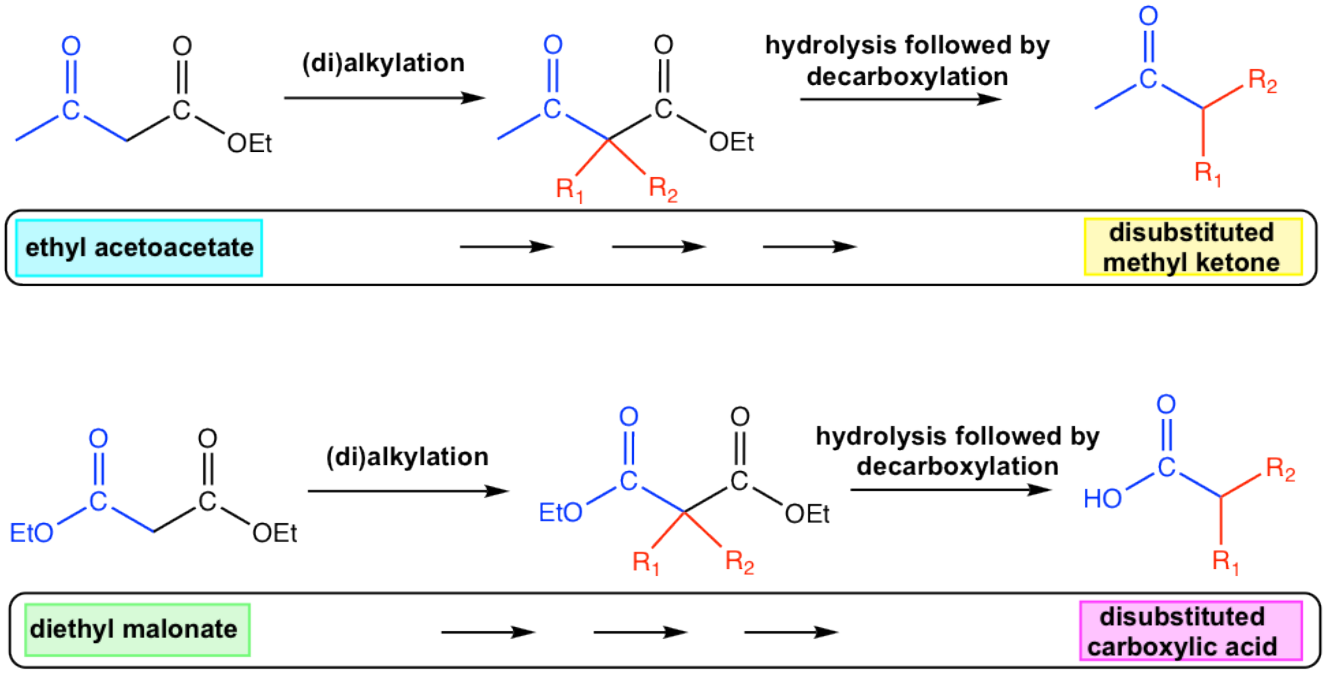
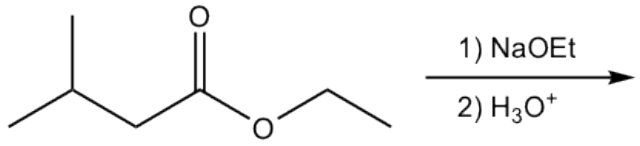


Fig. 8.3j. Summary of synthesis applications for ethyl acetoacetate and diethyl malonate

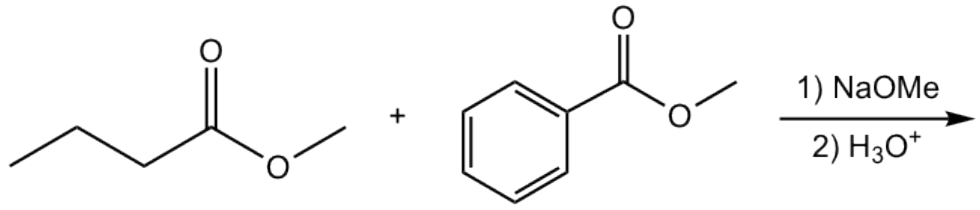
8.4 Practices

1. Show the major product(s) of the following reactions:

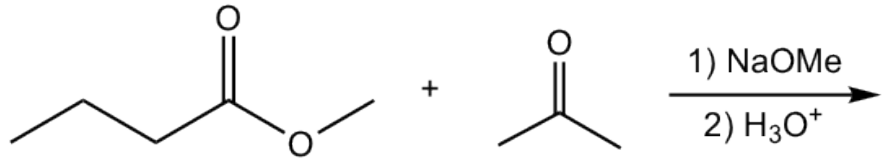
a.



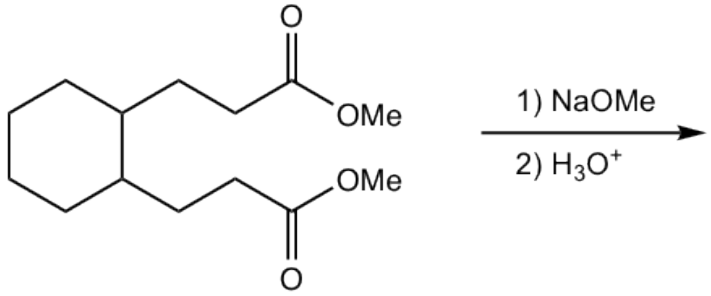
b.



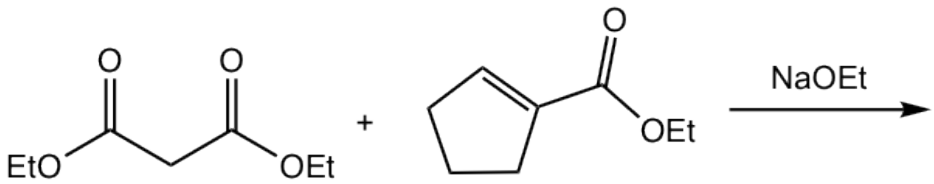
c.



d.

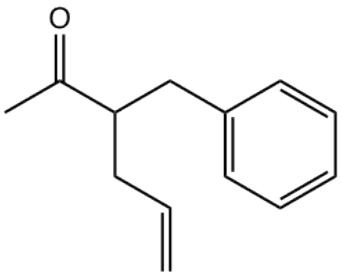


e.

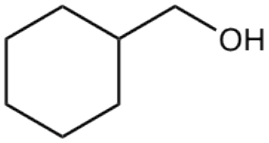


2. Design the synthesis route of the following compound from ethyl acetoacetate or diethyl malonate.

a.



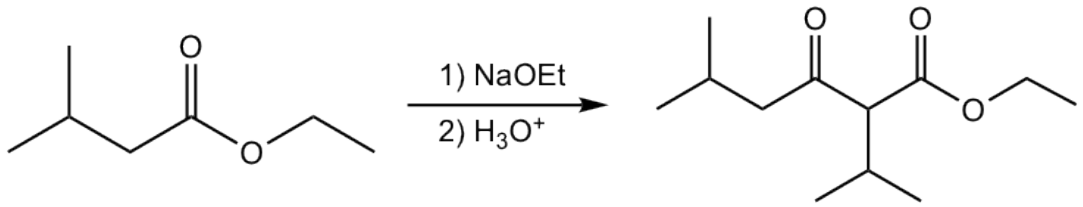
b.



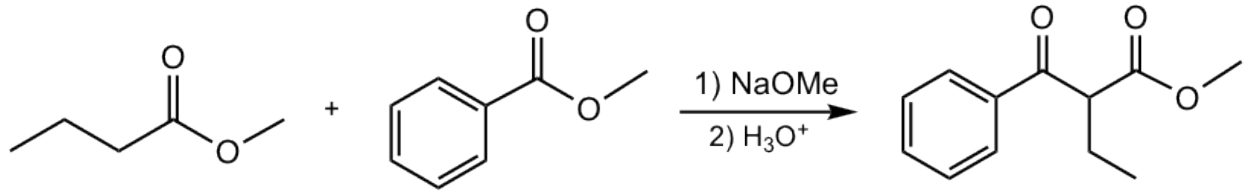
8.5 Practices Answers

1. Show the major product(s) of the following reactions:

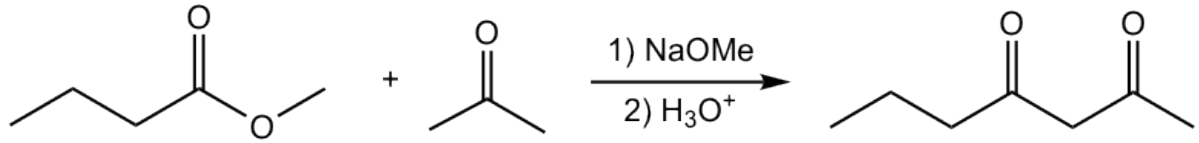
a.



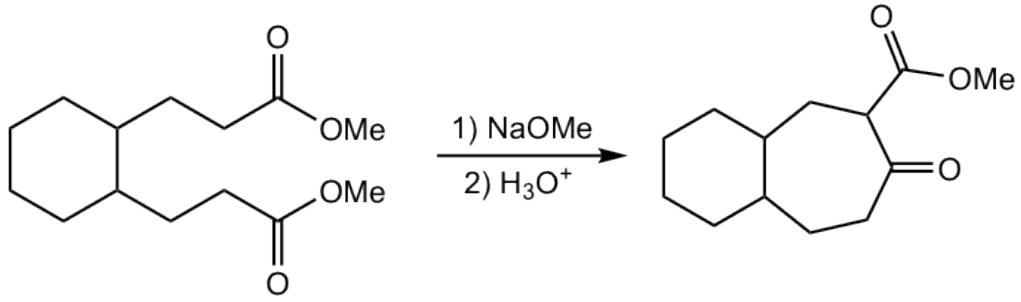
b.



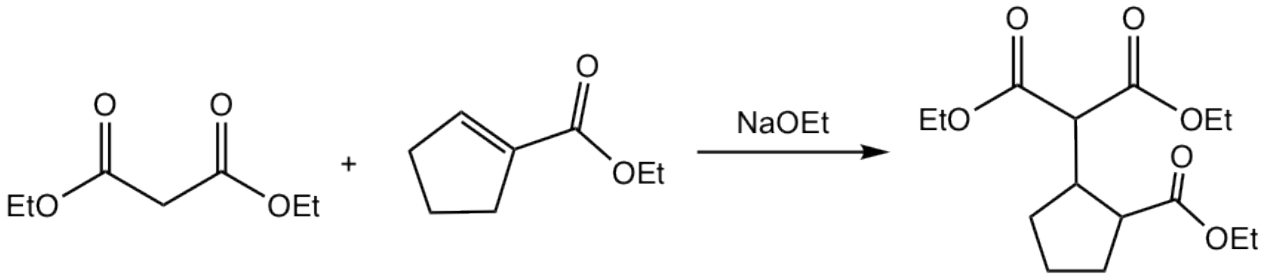
c.



d.

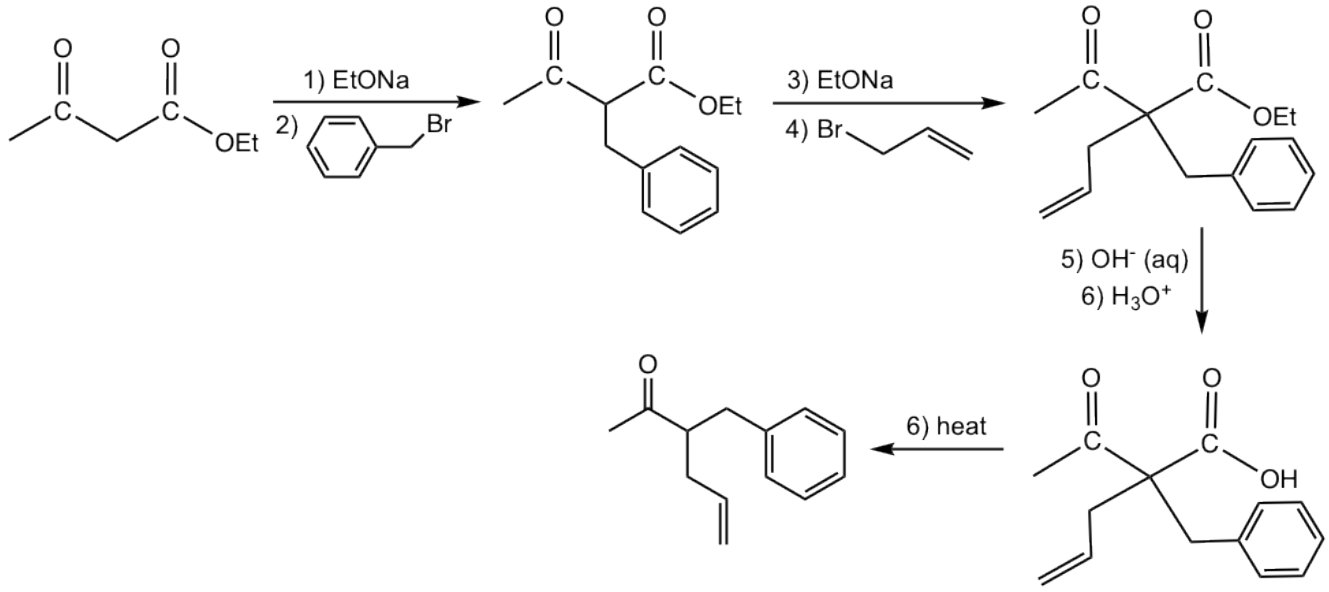


e.

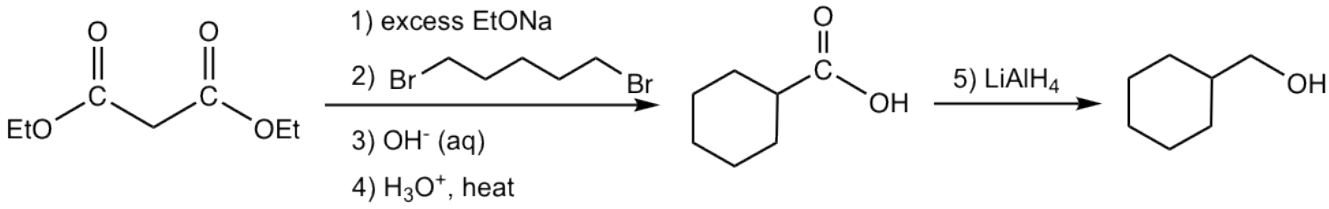


2. Design the synthesis route of the following compound from ethyl acetoacetate or diethyl malonate.

a.


1) EtONa
2)
Br
3) EtONa
4) Br
5) OH- (aq)
6) H3O+
6) heat
OEt
OH

b.


1) excess EtONa
2) Br
Br
3) OH- (aq)
4) H3O+, heat
5) LiAlH4
EtO
OEt
OH

CHAPTER 9: CARBOHYDRATES

Carbohydrate is a group of organic compounds found in biological systems. As the most abundant class of bioorganic compounds, carbohydrates make up more than 50% of the dry weight of the Earth's biomass. The formulas of many carbohydrates can be written as $C_n(H_2O)_n$, which makes them appear to be hydrates of carbon, which is also the origin of the name, although later structural studies indicate that these compounds are not hydrates. Nearly all carbohydrates taste sweet, such as sucrose (table sugar). Sugar is the common way people name small size carbohydrates in daily life. Aside from the sugars and starches that serve as a major source of metabolic energy, carbohydrates are also important structural materials (cellulose), recognition sites on cell surfaces, and one of three essential components of DNA and RNA.

9.1 Classification and Configurations of Carbohydrates and Monosaccharides

Carbohydrates are *polyhydroxy aldehydes* and *polyhydroxy ketones*, and compounds formed by linking *polyhydroxy aldehydes* or *polyhydroxy ketones* together. The term carbohydrate and saccharide could be used interchangeably. Saccharide comes from the word for sugar in several early languages, for example, *sakcharon* in Greek and *saccharum* in Latin.

The simplest carbohydrates are called **monosaccharides**. The complex carbohydrates contain two or more monosaccharides linked together. **Disaccharides** have two monosaccharides, **trisaccharides** have three monosaccharides, and so on. **Oligosaccharides** have 2-10 molecules of monosaccharides, and **polysaccharides** have 10 or more monosaccharides. Complex carbohydrates can be broken down into monosaccharides by hydrolysis.

9.1.1 Classification of Monosaccharides

Monosaccharides can be classified in different ways, which is summarized in Table 9.1.

- By the number of carbon atoms present in the molecule.
- Whether the molecule contains an aldehyde or a ketone functional group. The monosaccharide containing an aldehyde group is called an **aldose**, and one containing a ketone group is called a **ketose**.
- Pyranose and furanose for cyclic structure of monosaccharide, refer to section 9.2 for details.

	3-carbon	4-carbon	5-carbon	6-carbon	7-carbon
	Triose	**Tetrose**	**Pentose**	**Hexose**	**Heptose**
Aldehyde:	Aldotriose	Aldotetrose	Aldopentose	Aldohexose	Aldoheptose
Ketone:	ketotriose	ketotetrose	ketopentose	ketohexose	ketoheptose

Table 9.1 Classification of monosaccharides

9.1.2 The D and L Notation and Configurations of Monosaccharides

The simplest monosaccharides have three carbons, they are glyceraldehyde (aldotriose) and dihydroxyacetone (ketotriose). They are also the only two saccharides whose names do not end in “ose”. Glyceraldehyde has one chirality center, and dihydroxyacetone has no chirality center.

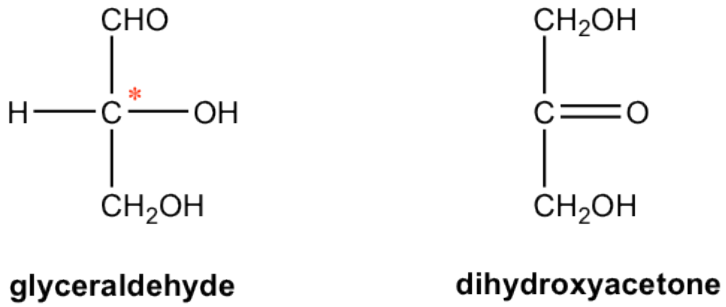


Fig. 9.1a The structure of glyceraldehyde and dihydroxyacetone

Since there is one chirality center in the glyceraldehyde, it has two enantiomers. The structures of both enantiomers are shown in Fig. 9.1b in Fisher projection, with configuration and optical rotation designation for each given as well. The R/S designation is determined according to the Cahn-Ingold-Prelog rule (refer to section??? Book I), and (+) and (-) for optical activity come from experimental results. Fischer projection is the most common way employed in carbohydrate chemistry to show the chemical structures of open-chain saccharides, in which chirality center(s) are usually involved.

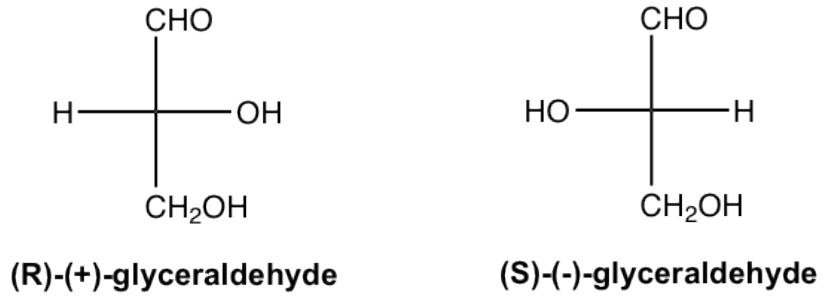


Fig. 9.1b Two enantiomers of glyceraldehyde

Early in the twentieth century, before the absolute configuration of any organic compounds could be determined, another system of stereochemical designation was introduced for monosaccharides. In this system, the carbonyl group is always placed on top (for aldose) or as close to the top as possible (for ketose) in a Fisher projection. If the OH group attached to the bottom-most chirality center (the carbon second from the bottom) is on the right side of the Fisher projection, the compound is a **D-saccharide**. If that OH group is on the left of the Fisher projection, the compound is a **L-saccharide**. Based on the D/L designation, the R-glyceraldehyde is the D-glyceraldehyde, and the S-glyceraldehyde is the L-glyceraldehyde. The D/L notation of stereochemical designations is thoroughly employed in carbohydrate chemistry, we will follow this convention in this book as well.

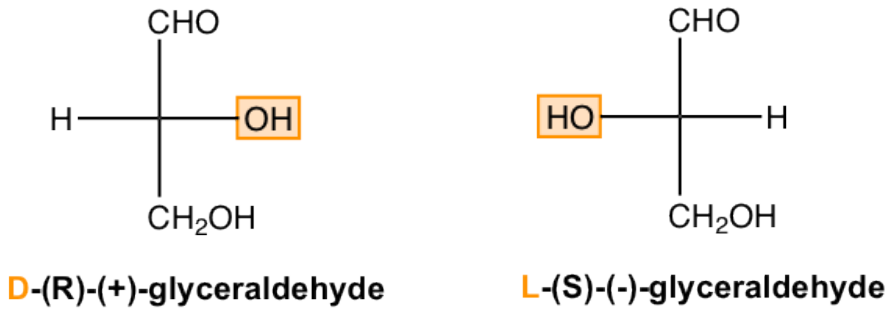


Fig. 9.1c D- and L-glyceraldehyde

There are several points to be noted for the D and L notations:

- D-monosaccharide and L-monosaccharide are mirror images, or enantiomers, to each other.
- Almost all sugars found in nature are D-saccharides.
- Like R/S, the D/L notations only indicate the configuration of the chirality center for the compound, they do not indicate the optical activity of the compound. As such, there is no correlation between D/L and (+)/(-).

Aldoses

For aldotetrose, there are two chirality centers and therefore four stereoisomers. As shown in Fig. 9.1d, two of them are D-sugars, and two are L-sugars. Each aldotetrose has its name.

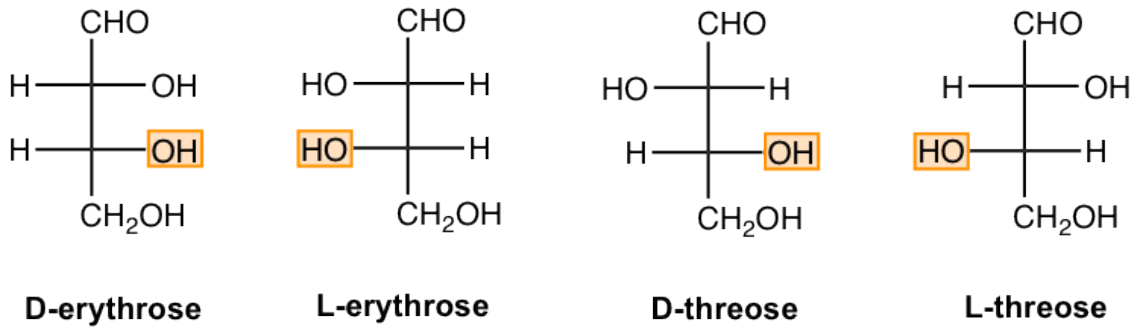


Fig. 9.1d The structures of D- and L-aldotetroses

With the number of carbons increasing to 5 (aldopentose) or 6 carbons (aldohexose), the number of diastereomers increases to eight and sixteen respectively. The monosaccharides (up to six carbons) belonging to the **D-family** are shown in the Fig. 9.1e below. The D-(+)-glucose is the most common example.

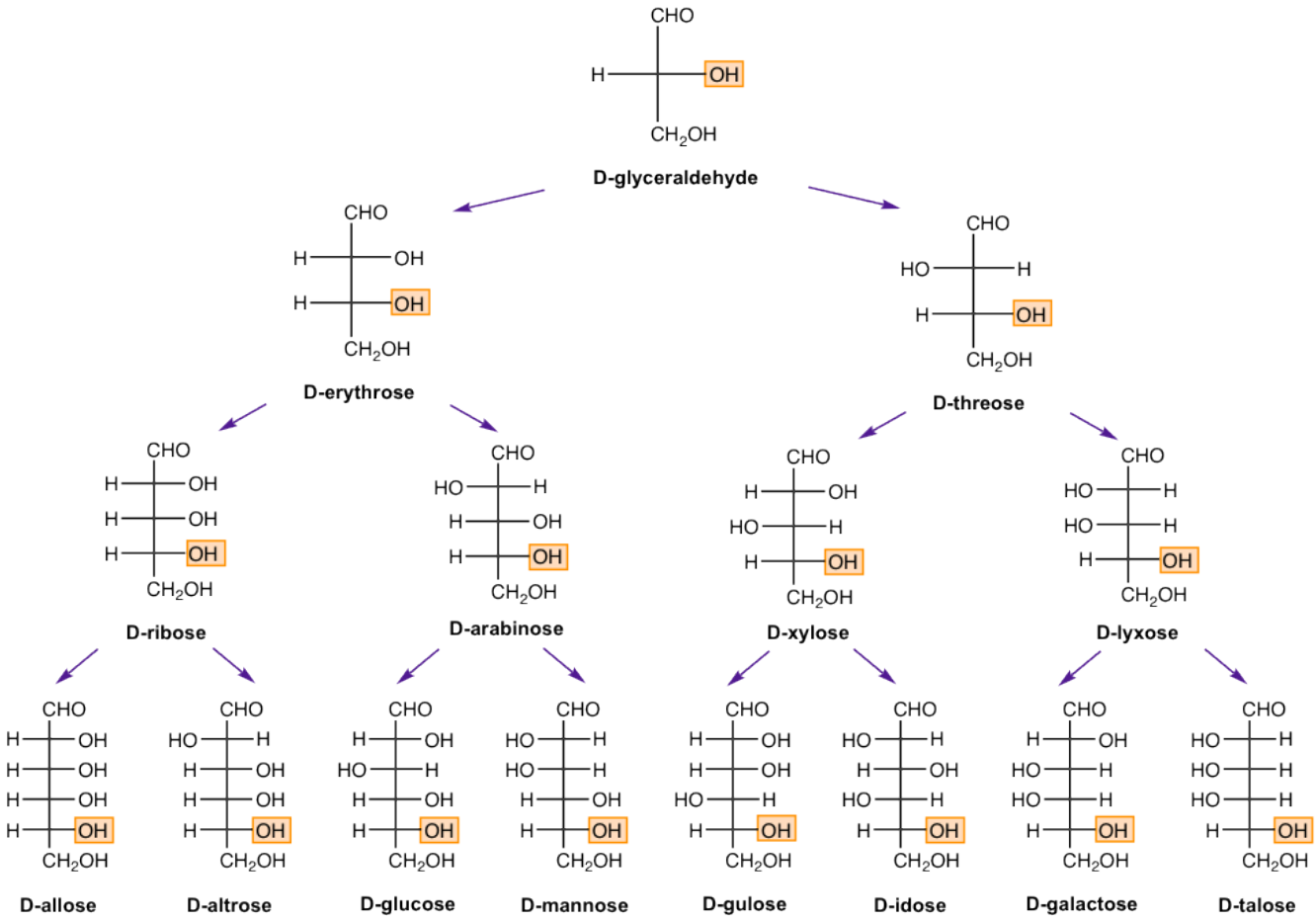


Fig. 9.1e The structures of D Family aldoses from three to six carbons

The diastereomers that differ in configuration at only one chirality center are called **epimers.** For example, D-glucose and D-mannose are C-2 epimers, and D-glucose and D-allose are C-3 epimers.

Ketoses

Carbohydrates that have a ketone group at the C-2 position are called ketoses. A ketose has one less chirality center than an aldose with the same number of carbons. The structures of D-ketoses up to six carbons are shown in Fig. 9.1f. D-fructose is the sugar that exists in fruits.

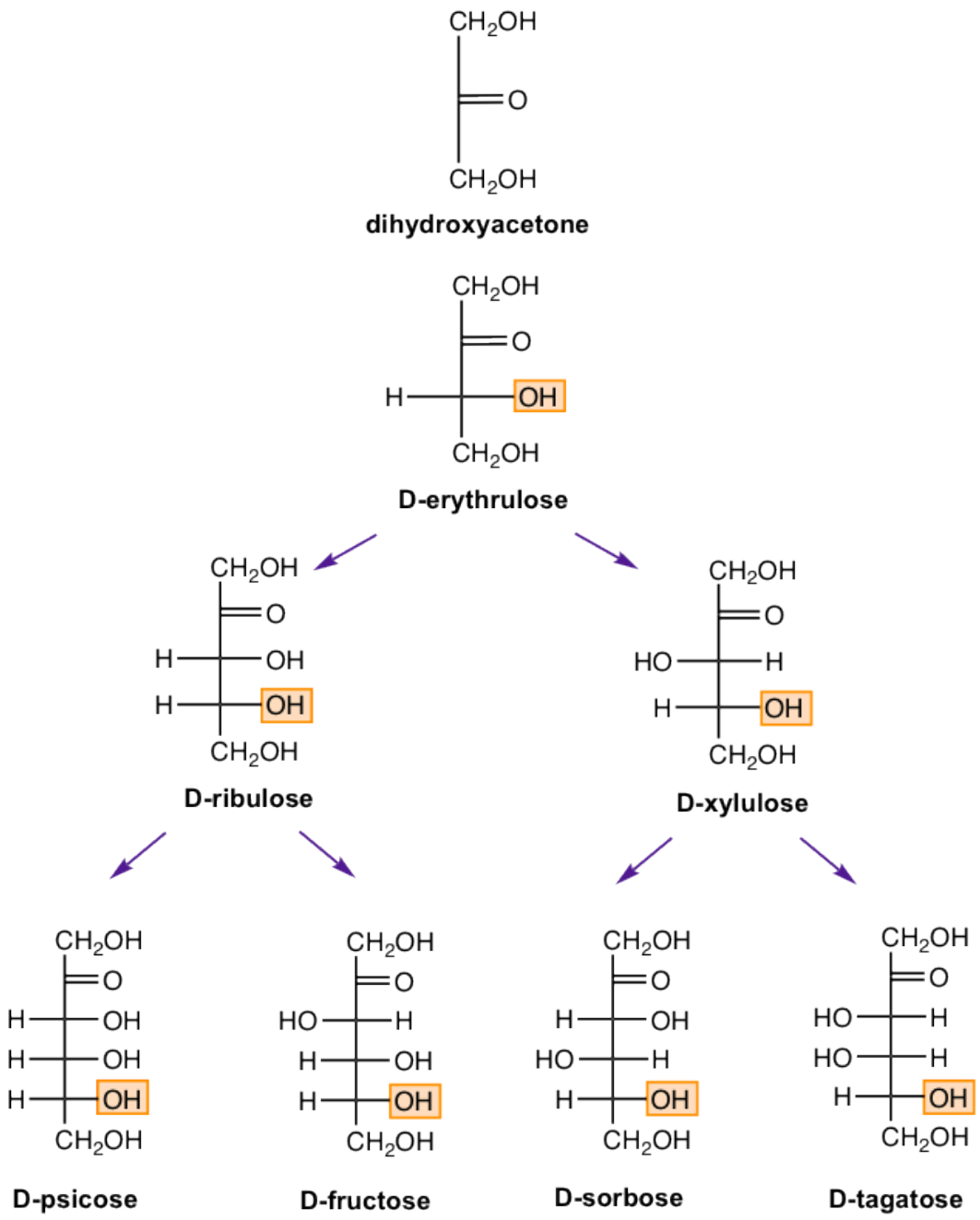


Fig. 9.1f The structures of D Family ketoses from three to six carbons

9.2 The Cyclic Structure of Monosaccharide and Mutarotation

The structure of monosaccharides has two categories: the open-chain form and the cyclic form. The discussions in previous sections focused on the open-chain form, and we will start with D-glucose as an example here to illustrate the cyclic form structures, and the correlation between the two types of structures.

9.2.1 The Cyclic Structures of Monosaccharide

The reason why D-glucose exists in cyclic form is that the molecule contains both aldehyde and alcohol functional groups. The intramolecular reaction between the aldehyde group (on C-1) and the OH group on C-5 forms the six-membered cyclic hemiacetal functional group (refer to **section 2.5** for the formation of hemiacetal).

The detailed process of converting from open-chain D-glucose in Fisher projection to cyclic form is shown in Fig. 9.2a diagram.

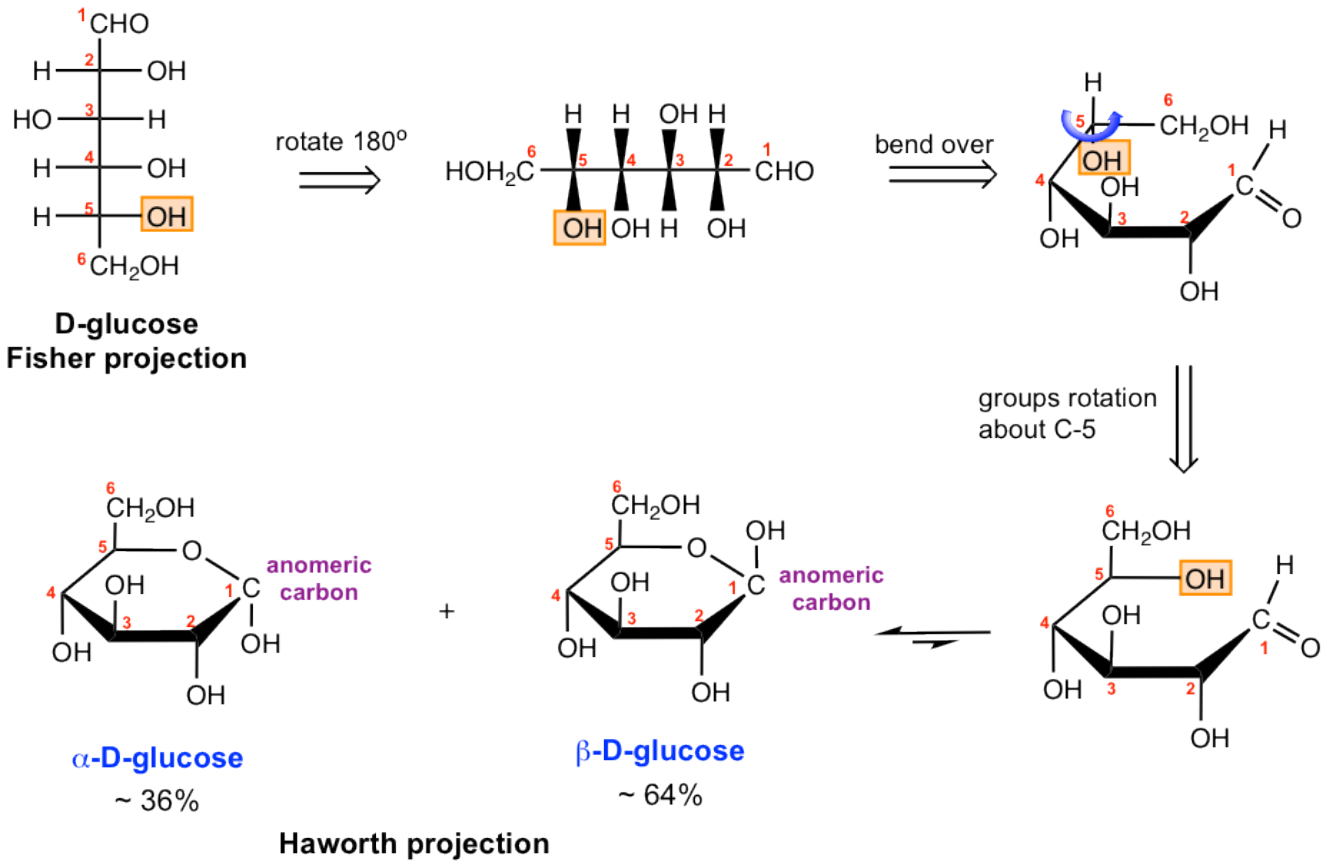


Fig. 9.2a D-glucose: from Fisher projection to cyclic hemiacetal in Haworth projection

To make it easier for us to see the correlation between open-chain and cyclic structure, the Fisher projection is first rotated 90° and re-drawn horizontally (please note that this drawing is not a Fisher projection anymore). The structure is then bent over to mimic a flat ring structure, with the groups on the right side in the Fisher projection point **down** in the "ring", and the groups on the left side in the Fisher projection point **up** in the "ring". Next, the groups around C-5 are rotated so that the CH_2OH group points "up" and the OH group stays "flat", as a result, the OH group is in a "convenient" position to react with the aldehyde group on C-1 and forms the six-membered hemiacetal ring. The structure then could be easily converted to the ring structure. With the formation of the hemiacetal group, C-1 is a newly generated chirality center in the ring that could have two possible configurations. Therefore two diastereomers exist for the cyclic hemiacetal and they are called α-D-glucose (OH group points down of the ring, and *trans* to the CH_2OH group) and β-D-glucose (OH group points up of the ring, and *cis* to the CH_2OH group) respectively. In carbohydrate chemistry, the diastereomers differing only at the hemiacetal (or acetal) carbon are called **anomers**, and the hemiacetal (or acetal) carbon is called the **anomeric carbon**. α-D-glucose and β-D-glucose are two anomers of D-glucose. The prefixes α and β are always used to denote the configuration of the anomers in carbohydrate chemistry.

The way of six-membered ring hemiacetal shown above is called the **Haworth projection.**

Studies of the structure of the cyclic hemiacetal of the D-glucose have demonstrated that the actual conformation of the rings is the chair conformation similar to cyclohexane. Almost all the large substituents, OH and CH_2OH, are ***equatorial*** in the chair conformations of D-glucose, except on the anomeric carbon for α anomer, as you would expect. In carbohydrate chemistry, both Haworth projections and chair conformations are commonly used to represent the structures of the cyclic form sugars.

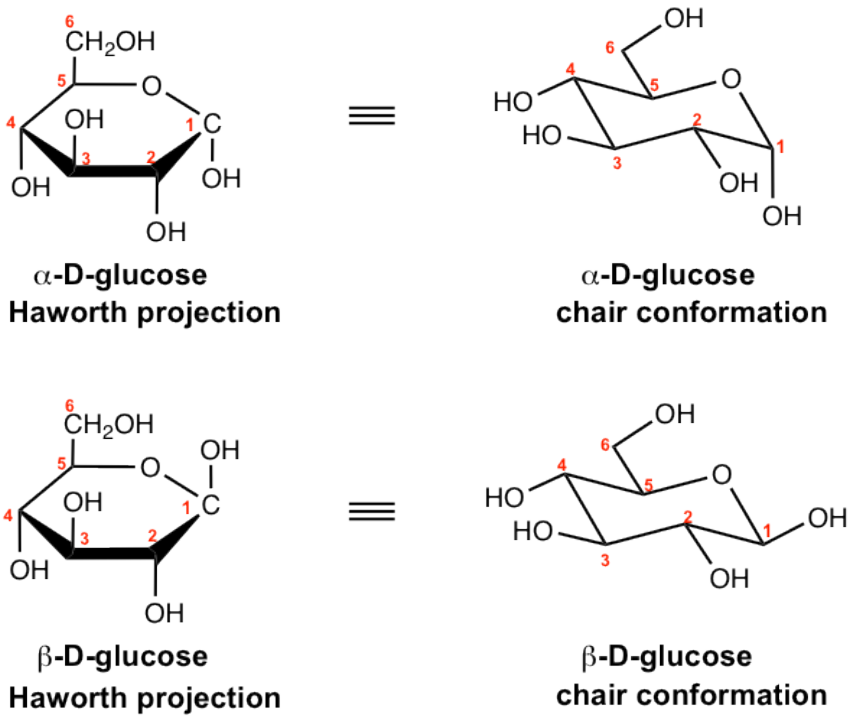


Fig. 9.2b Cyclic D-glucose in chair conformations

Other than six-membered rings, five-membered rings are also common for cyclic forms of monosaccharides. D-ribose, the pentose, for example, forms the five-membered-ring hemiacetal, again in both α and β anomers.

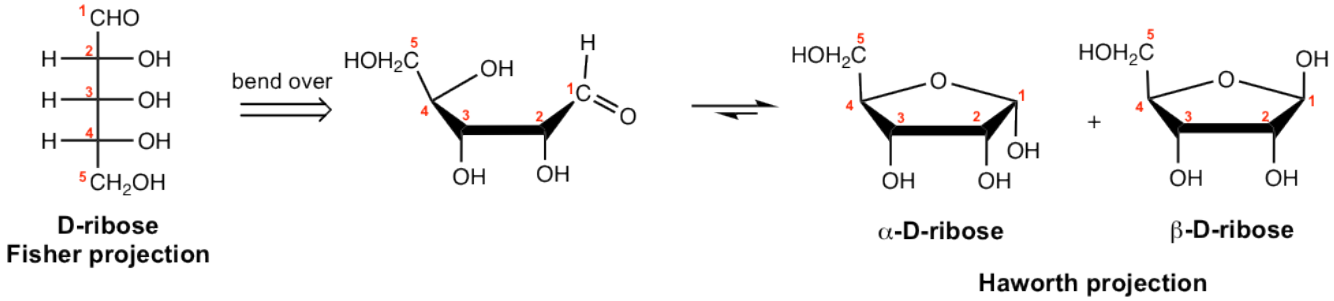


Fig. 9.2c D-ribose in five-membered cyclic hemiacetal structures

A six-membered cyclic monosaccharide is called a **pyranose**, and a six-membered cyclic monosaccharide is called a **furanose**. These names come from the names of heterocyclic compounds **pyran** and **furan**, as shown in Fig. 9.2d.

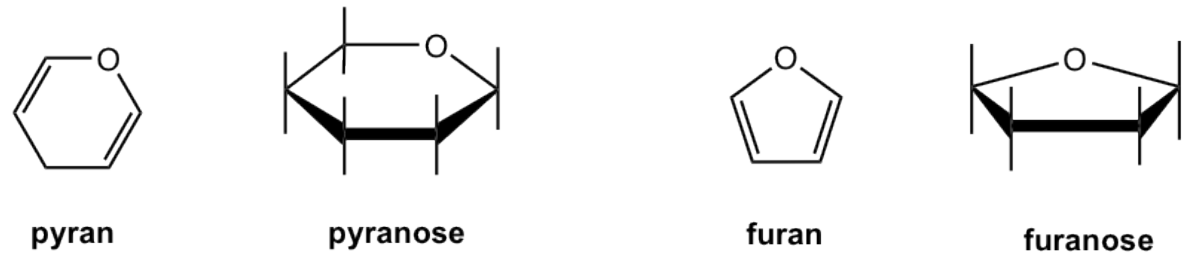


Fig. 9.2d Structure template of pyranose and furanose

Thus, the full name of the β-D-glucose, for example, is β-D-glucopyranose. A couple more examples of cyclic monosaccharides are given below with the full names.

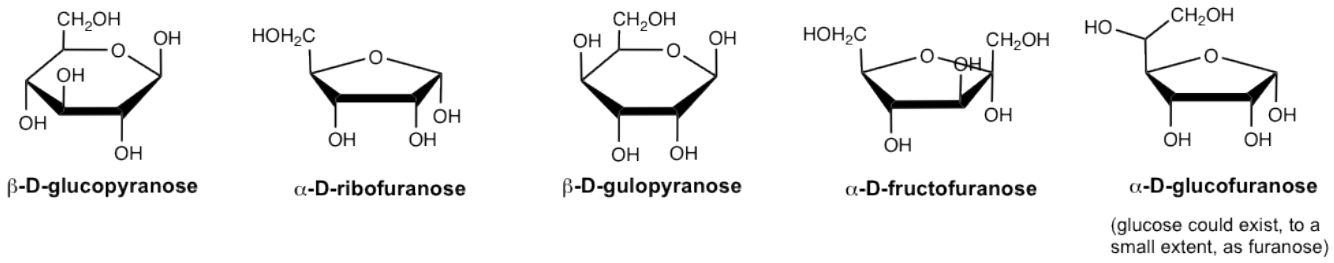


Fig. 9.2e Structures and names of pyranose and furanose examples

9.2.2 Mutarotation

As we have learned D-glucose exists in three forms, the open-chain form and two cyclic forms (α and β anomers).

Further studies indicated that pure α-D-glucopyranose has a specific rotation of +112°, and β-D-glucopyranose has a specific rotation of +18.7°. However, when crystals of pure α-D-glucopyranose are dissolved in water, the optical rotation of the solution changes gradually from +112° to +52.7°. Similar observations apply to the solution of pure β-D-glucopyranose as well, with the optical rotation of the solution changing gradually from +18.7° to +52.7°. This slow change in optical rotation toward an equilibrium value is called **mutarotation**.

The explanation for the mutarotation lies in the existence of an equilibrium between the open-chain form and the α and β forms of the cyclic hemiacetals in water, as shown below with the cyclic forms in both Haworth projections and chair conformations for your comparison.

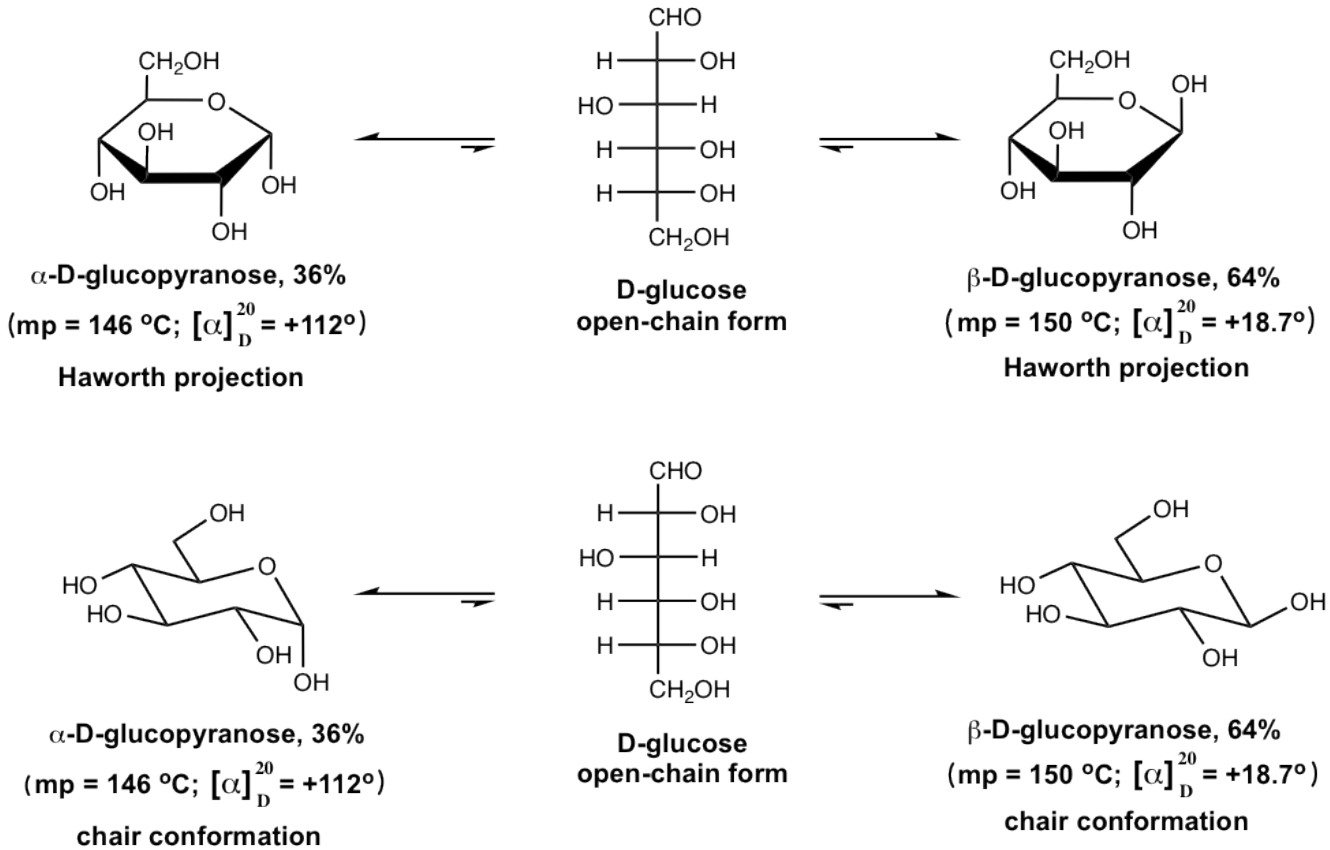


Fig. 9.2f Equilibrium between different forms of D-glucose

In solution, the hemiacetal ring opens to form the open-chain form, and the open-chain form recyclizes to form cyclic hemiacetals, till an equilibrium is reached with a certain concentration/amount of each form present. The concentration of open-chain form in solution at equilibrium is very small for D-glucose, which is about 0.02%. This is supported by the evidence that the IR of the solution of D-glucose has no band for a carbonyl group. Assuming that the amount of open-chain form is negligible, the percentages of each cyclic form can be calculated based on the specific rotation for each (+112° for α, and +18.7° for β), and the observed rotation for the solution at equilibrium (+52.7°). The higher percentage of β anomer, which is 64%, can be explained by the higher stability of β-D-glucopyranose with all the groups in equatorial positions.

9.2.3 Glycoside Formation

When D-glucopyranose reacts with alcohol under acidic conditions, the reaction takes place and the hemiacetal is converted to acetal on the anomeric carbon. The carbohydrate acetals are generally called **glycosides**. The glycoside products in the following reaction (Fig. 9.2g) are therefore named methyl D-glucopyranoside, with α and β anomers.

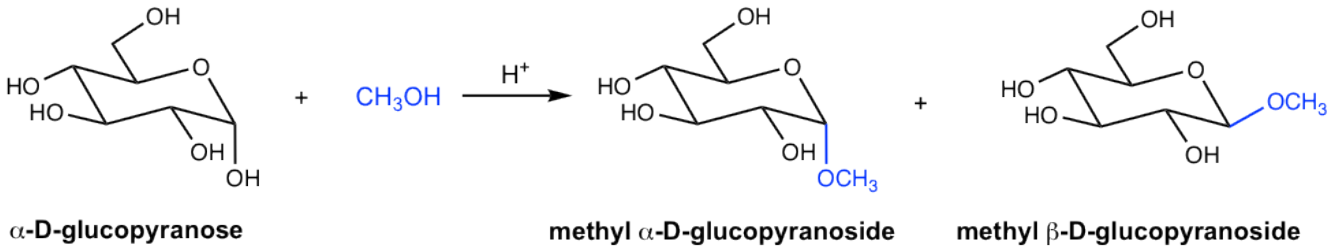


Fig. 9.2g Formation of methyl D-glucopyranosides

The mechanism for the formation of a glycoside (Fig. 9.2h) is pretty much the same as the general mechanism from hemiacetal to acetal (**section 2.5**) but in a cyclic structure here.

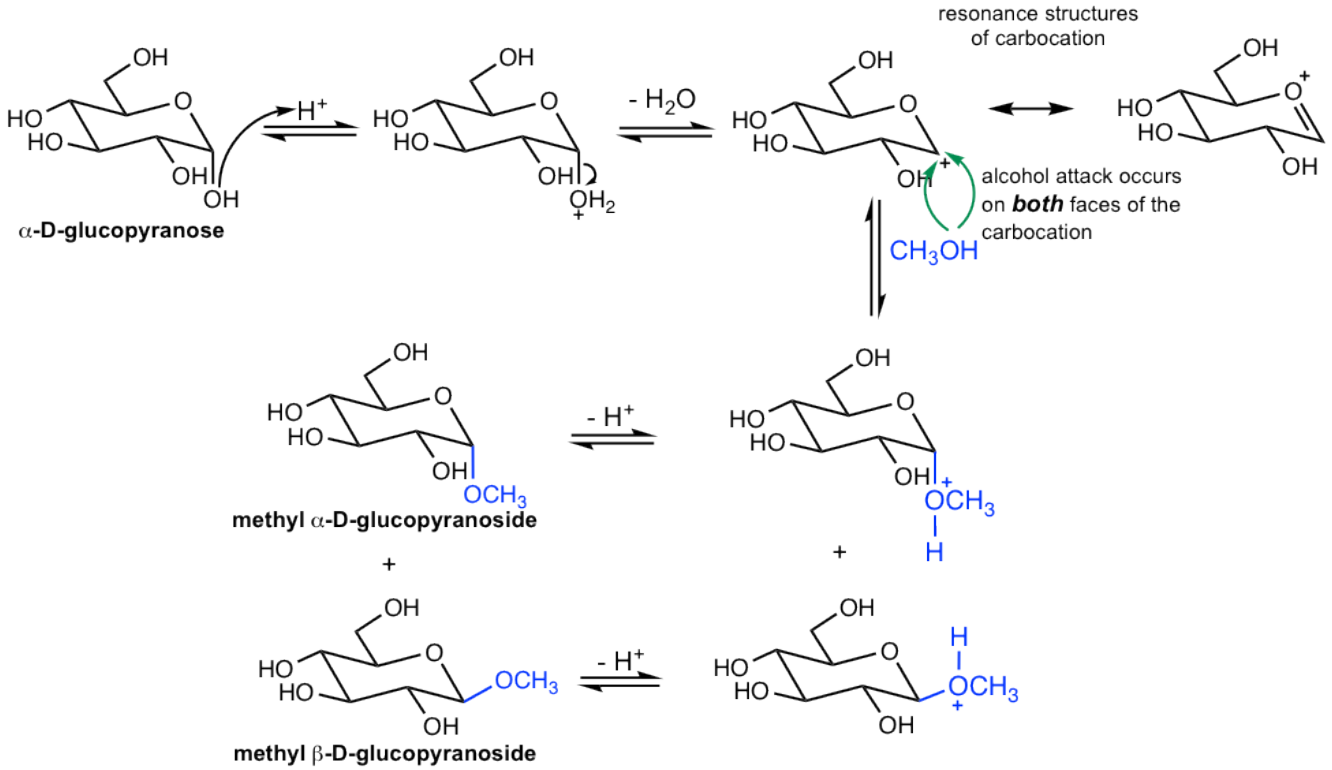


Fig. 9.2h Mechanism for the formation of glucopyranoside from glucopyranose

In the step of alcohol attack on the carbocation intermediate, which is stabilized by resonance effect, the attack occurs

on both faces of the planar carbocation, therefore leading to the formation of both α and β anomers, even though the reactant hemiacetal is the α anomer.

Glycoside, which is an acetal, is stable in basic conditions. Glycoside therefore is used as a common protection group of the anomeric carbon in basic condition, that is to prevent undesired reactions that would involve the anomeric carbon in its hemiacetal form.

In an acidic solution, glycosides undergo hydrolysis to give back sugar and alcohol. The reaction is essentially just the hydrolysis of acetal to hemiacetal.

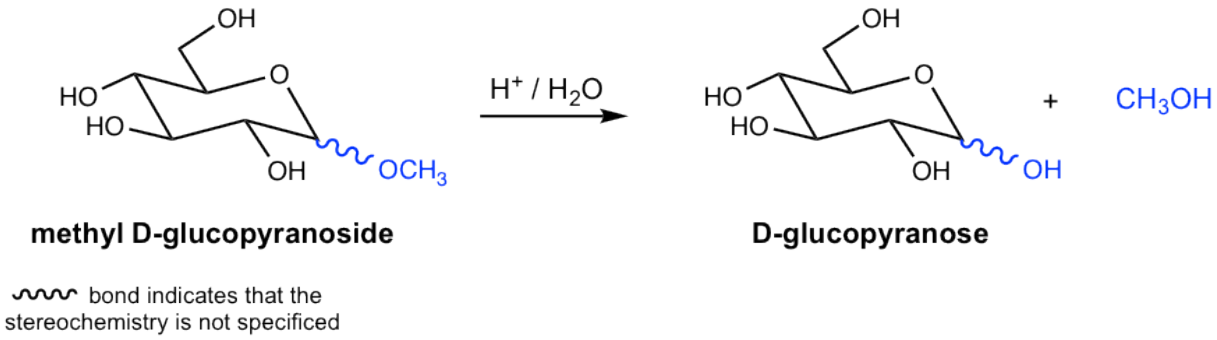


Fig. 9.2i Hydrolysis of glucopyranoside to glucopyranose

9.3 Other Reactions of Monosaccharides

9.3.1 Alkylation (Formation of Ethers)

The hydroxyl groups of monosaccharides can be converted to ethers by a couple of different conditions, and methyl ethers are prepared most commonly. The reagents that can be used to synthesize methyl ethers include:

- NaH and CH_3I
- NaOH and $(CH_3)_2SO_4$
- Ag_2O and CH_3I

Although different conditions could be applied, the reactions essentially go through S_N2 where the OH groups are deprotonated first and then react with methylation reagents. A couple of examples are given below.

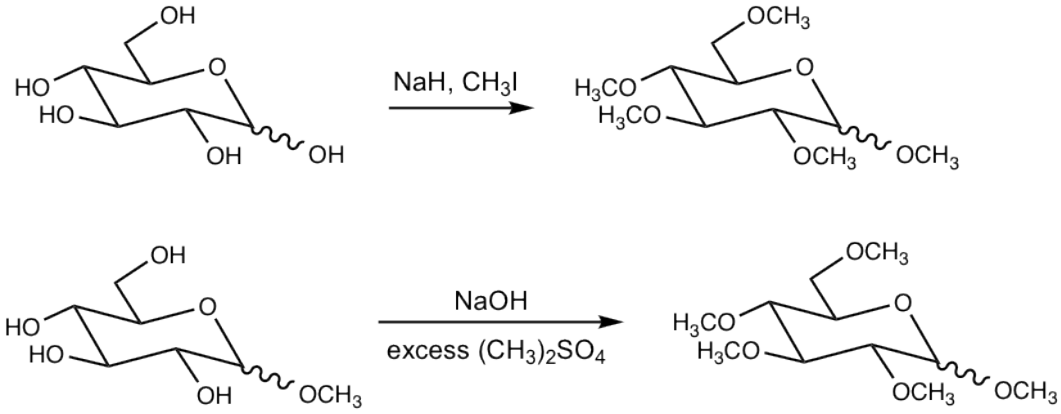


Fig. 9.3a Methylation reactions of D-glucopyranose

A specific note is that all the OH groups are methylated with the above conditions to produce pentamethyl derivative, while the reaction with CH_3OH/H^+ (in **section 9.2.3**) only converts the OH on anomeric carbon to OCH_3 (hemiacetal to acetal). On the other side, when the pentamethyl derivative of monosaccharide is treated in an acidic solution, only the methyl group on anomeric carbon is hydrolyzed because it is an acetal, and all the other ethers are not affected by aqueous hydrolysis.

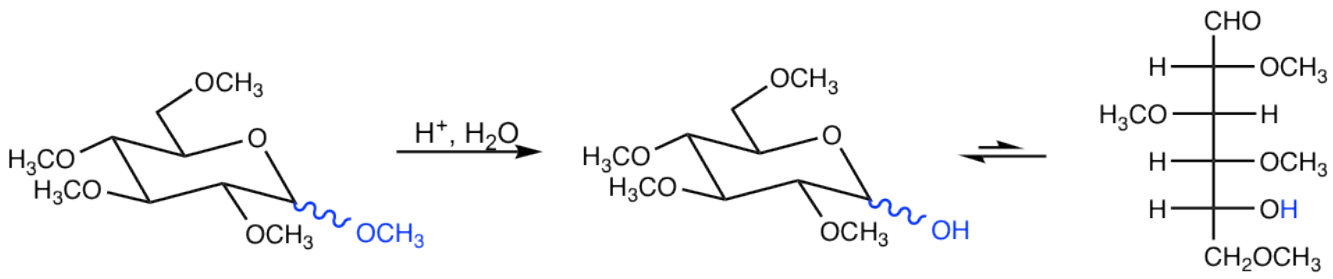


Fig. 9.3b Hydrolysis of pentamethyl D-glucopyranoside

9.3.2 Acylation (Formation of Ester)

The hydroxyl groups of monosaccharides can be converted to esters by reacting with excess anhydride, in the presence of a weak base (refer to **section 7.5.2**, the preparation of ester from anhydride).

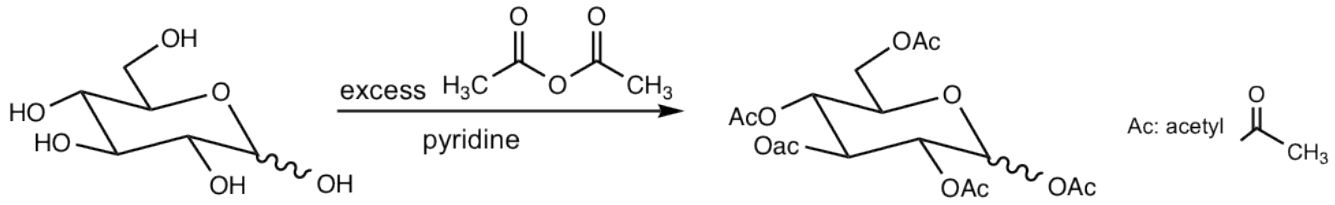


Fig. 9.3c Acylation of D-glucopyranose

9.3.3 Conversion to Cyclic Acetals

There are multiple hydroxyl groups in monosaccharides, and they are good candidates as 1,2-diol (or 1,3-diol) to produce cyclic acetals with aldehyde or ketone, as the example given in Fig. 9.3d. Such a reaction only occurs when the two OH groups are **cis** to each other in terms of the ring.

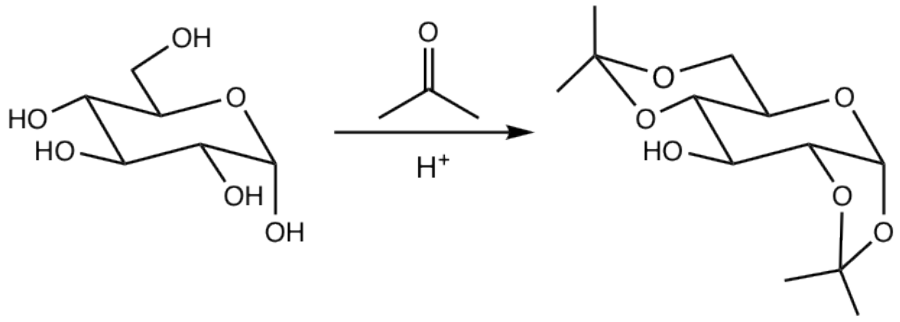


Fig. 9.3d Formation of cyclic acetal derivative of D-glucopyranose

9.4 Oxidation and Reduction Reactions of Monosaccharides

9.4.1 Oxidation with Bromine

Bromine, Br_2, is a mild oxidizing agent and oxidizes the aldehyde group in the aldose to the carboxylic acid group. The resulting compound is an **aldonic acid**. The aqueous solution of bromine, $Br_2(aq)$, is used for this oxidization with a pH in the range of 5~6. No isomerization and fragment reaction for monosaccharides occurs in such mild acidic conditions.

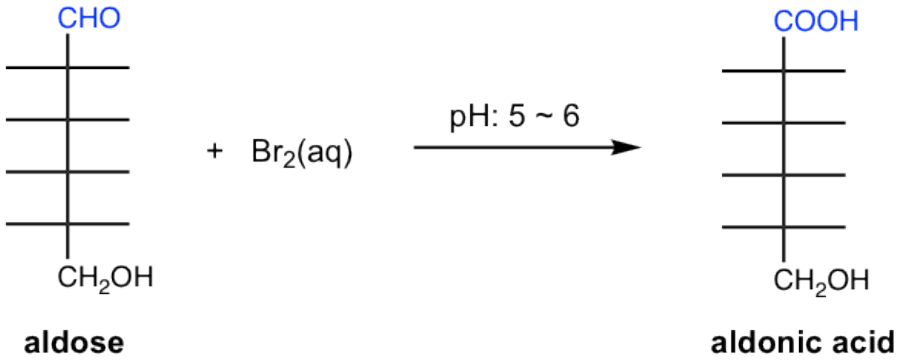


Fig. 9.4a Oxidation of aldoses with bromine (the OH groups on the middle carbons are skipped)

Ketoses are not oxidized by bromine water, as a result, this reaction can be used as a test to separate apart ketose and aldose. The disappearance of the reddish color for bromine water indicates the presence of aldose.

For aldose, the oxidation product aldonic acid may undergo a subsequent intramolecular esterification reaction, between COOH and the OH group on C-4, to form a γ-lactone, as shown in the following example.

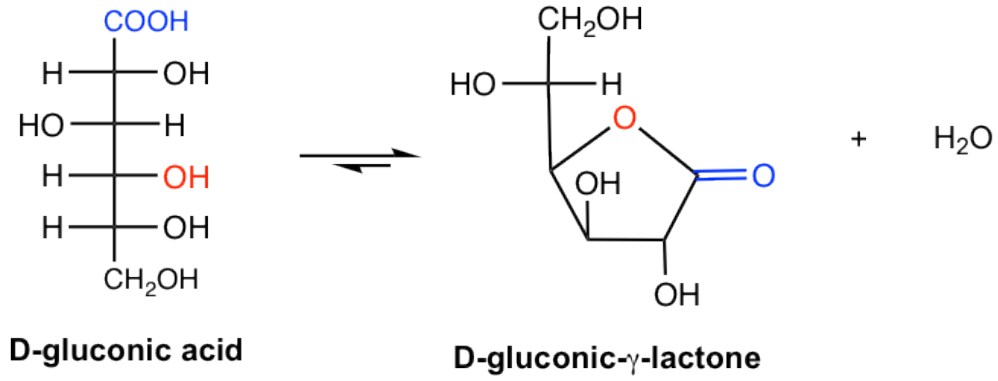


Fig. 9.4b Cyclization reaction of D-gluconic acid to D-gluconic-γ-lactone

9.4.2 Oxidation with Tollens' Reagent

Both aldoses and ketoses are oxidized to aldonic acids by Tollens' reagent. Tollens reagent is prepared by mixing $AgNO_3$ with aqueous ammonia solution and contains $Ag(NH_3)^+$ cation. Although the Tollens' reagent does not react with the ketone group directly, ketose undergoes isomerization in an alkaline solution to aldose, which is then oxidized by the Tollens' reagent.

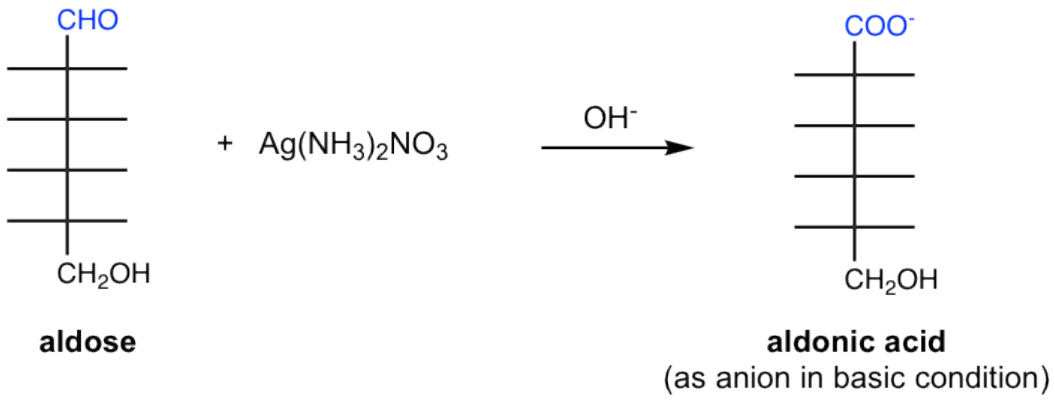


Fig. 9.4c Oxidation of aldoses with Tollens' reagent (the OH groups on the middle carbons are skipped)

Another oxidizing agent that contains Cu^{2+} is called Benedict's reagent. Both aldoses and ketoses are oxidized by Benedict's reagent as well, with a red precipitation of Cu_2O generated. The appearance of the red precipitation is an indication of the positive result of the reaction.

Fig. 9.4d Oxidation of aldoses and ketoses with Benedict's reagent

Carbohydrates that give positive tests with Tollens' reagent and Benedict's reagent are known as **reducing sugars**.

- Aldoses, ketoses, and carbohydrates that contain a *hemiacetal* group are reducing sugars.
- Carbohydrates that contain only *acetal* groups don't react with Tollens' and Benedict's reagents, and they are **nonreducing sugars**.

9.4.3 Oxidation with Nitric Acid HNO_3

Dilute nitric acid is a stronger oxidizing agent and oxidizes both the aldehyde group and the terminal CH_2OH group of an aldose to carboxylic acid groups, giving dicarboxylic acids that are known as aldaric acids.

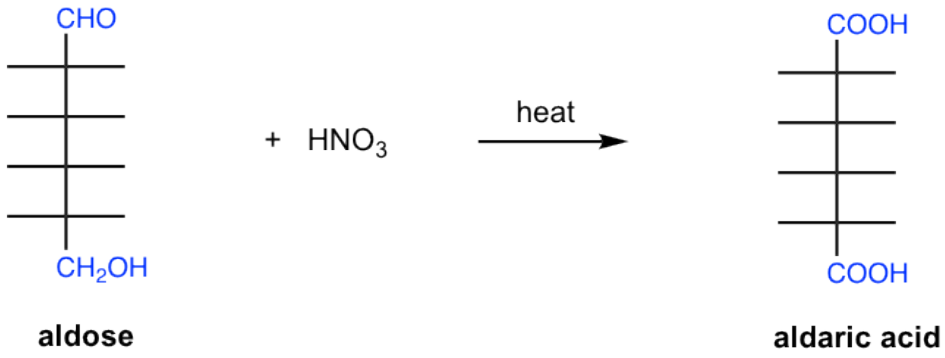


Fig. 9.4e Oxidation of aldoses with nitric acid (the OH groups on the middle carbons are skipped)

9.4.4 Periodate Oxidation

Periodate, HIO_4, oxidizes compounds containing OH groups on adjacent carbons in a way called oxidative cleavage, that is, to break the C-C bonds and produce carbonyl compound products. We will examine the reaction with several types of structures involved.

- Two adjacent -CHOH groups react with one equivalent of HIO_4, to generate two carbonyl compounds.

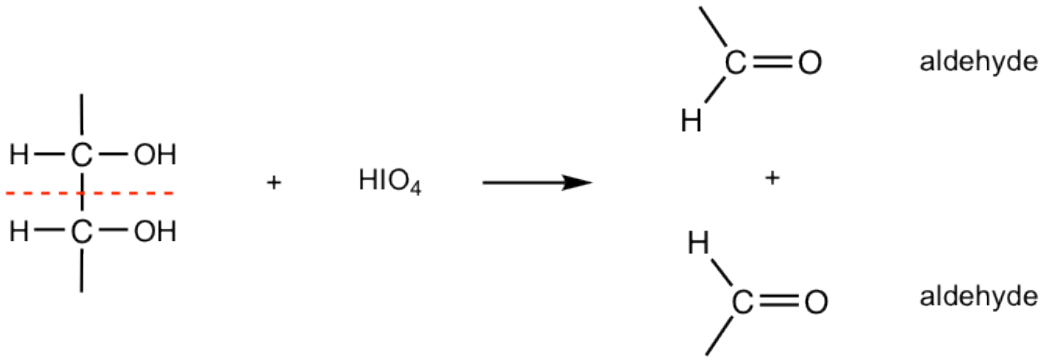


Fig. 9.4f Oxidation of two adjacent -CHOH groups with periodate

- Oxidative cleavage also takes place when an OH group is adjacent to the carbonyl group of an aldehyde or ketone.

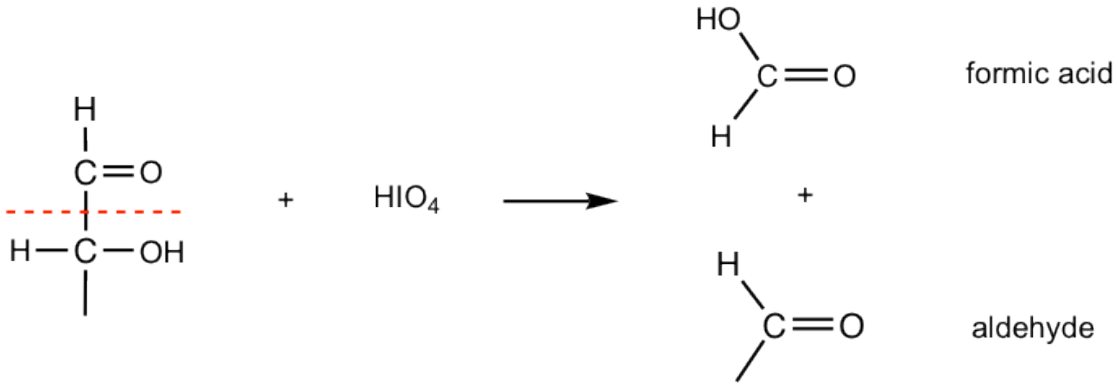


Fig. 9.4g Oxidation of adjacent C=O and CHOH groups with periodate

Please note that for every C-C bond cleavage, a C-O bond is formed at each carbon. With the extra C-O bond "added" onto the C=O carbonyl group, the carboxylic acid, COOH, is produced.

- When there are three or more contiguous -CHOH groups, the internal ones are obtained as carboxylic acid. This can be explained in the way that the internal carbon undergoes bond cleavage twice, it converts to C=O at first, then converts to COOH after the second time cleavage.

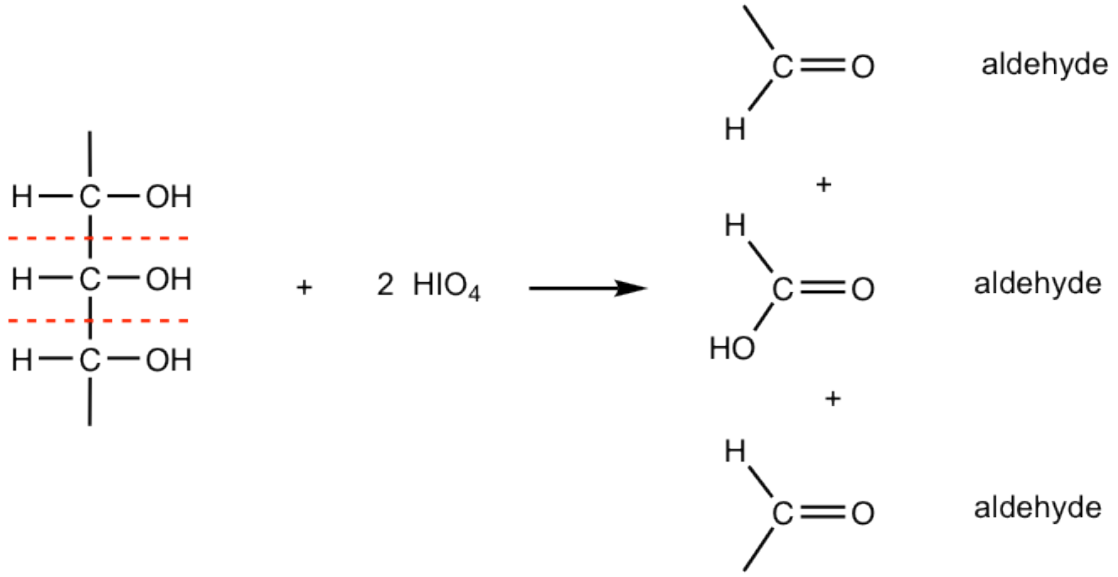
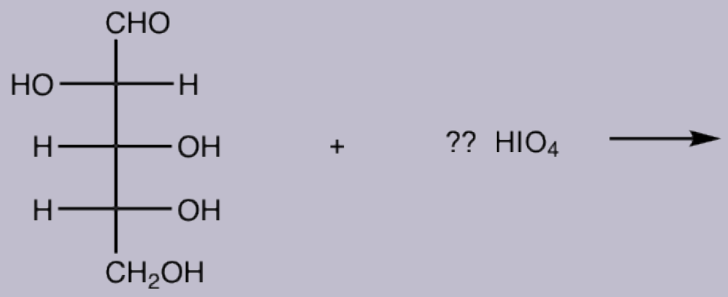


Fig. 9.4h Oxidation of three adjacent CHOH groups with periodate

Please note that each C-C bond reacts with one equivalent of HIO_4, therefore two equivalents of HIO_4 are required for three contiguous -CHOH groups (or C=O groups), three equivalents of HIO_4 are required for four contiguous -CHOH groups (or C=O groups), and so on.

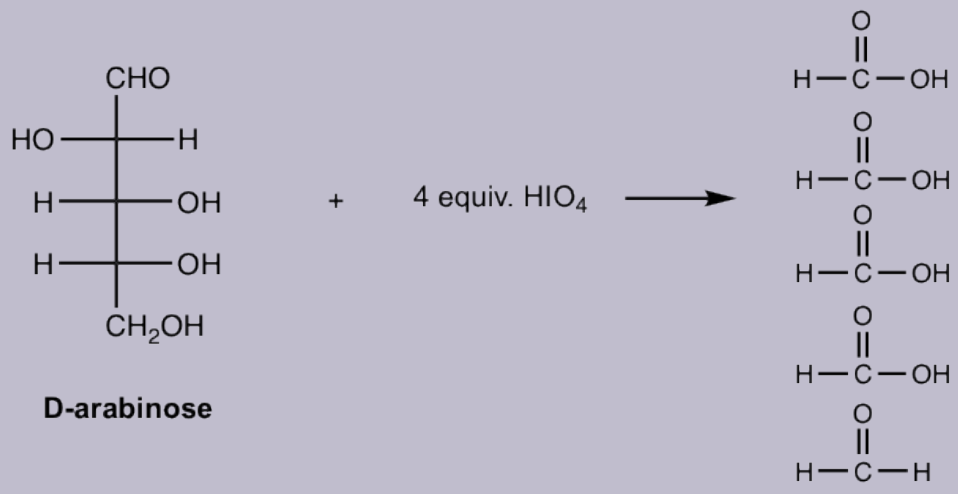
Examples

For the reaction of D-arabinose with HIO_4, indicate the amounts of HIO_4 required and show all the products.



D-arabinose

Answer:



D-arabinose

9.4.5 Reduction with $NaBH_4$

The carbonyl group in aldoses and ketoses can be reduced by sodium borohydride, $NaBH_4$, to produce polyalcohol which is known as **alditol**. Reduction of aldose forms one alditol product as shown in Fig. 9.4i.

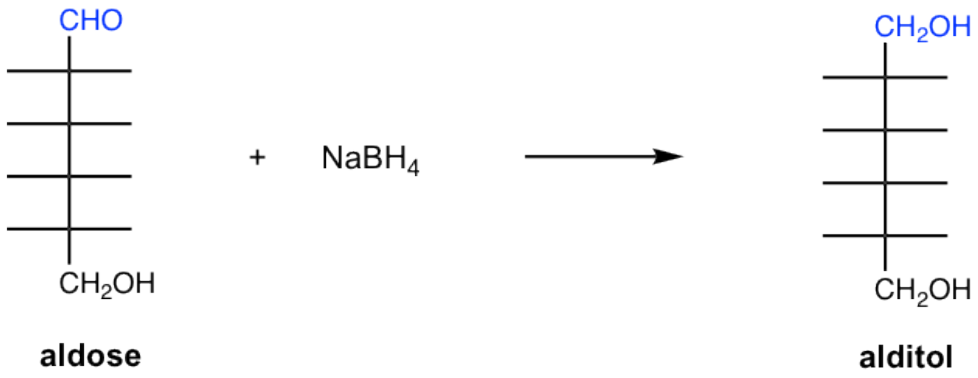


Fig. 9.4i Reduction of aldoses with sodium borohydride (the OH groups on the middle carbons are skipped)

For the reduction of ketoses, however, two alditols are formed because the reduction creates a new chirality center and both stereoisomers are possible. The reduction of D-fructose is given as an example in Fig. 9.4j, in which both D-mannitol and D-Glucitol are produced.

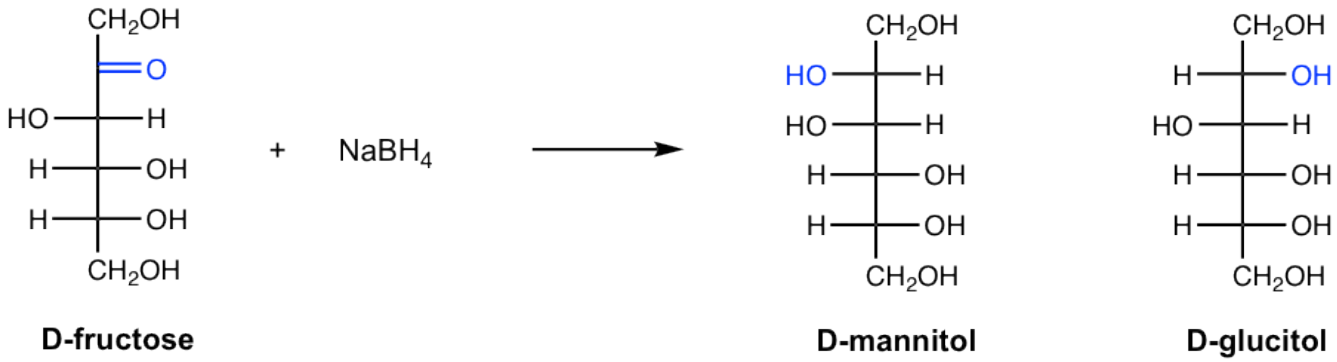


Fig. 9.4j Reduction of D-fructose with sodium borohydride

9.4.6 Osazones: Reaction of Monosaccharides with Phenylhydrazine

Since aldoses or ketoses have the carbonyl group, they also react with phenylhydrazine, but in a different way than that of common aldehyde or ketone. Aldoses and ketoses react with three equivalents of phenylhydrazine to produce a type of compound called **osazones**. The osazone derivatives of monosaccharides are crystalline solids that are insoluble in water, and could be easily isolated and purified, they were once used to identify monosaccharides.

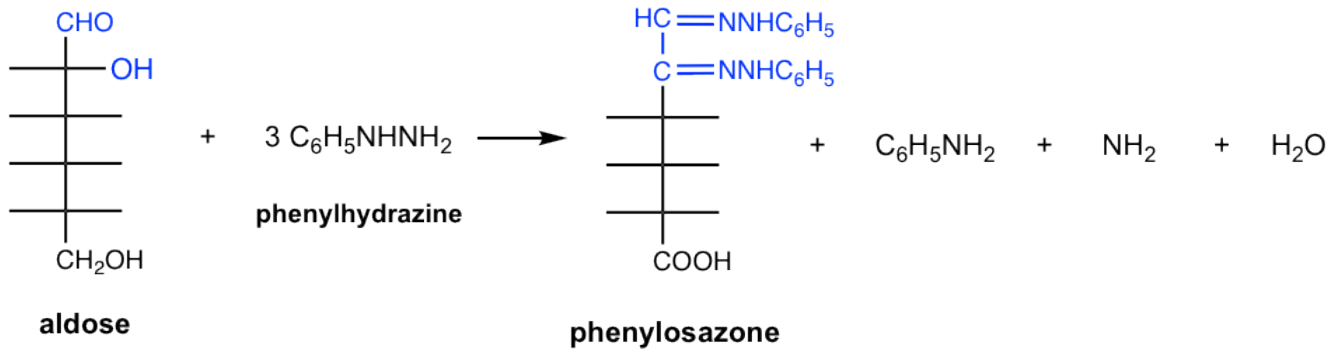


Fig. 9.4k Formation of osazone between aldose and hydrazine (the OH groups on the middle carbons are skipped)

The simplified way to understand why three equivalents of phenylhydrazine react with aldose or ketose is that one equivalent oxidizes the OH group (the OH at C-2 for aldose, the OH at C-1 for ketose) to a carbonyl group, and two equivalents react with two carbonyl groups to form two imines. The actual mechanism is more complicated though.

Since C-2 in osazone is not chiral carbon, two aldoses that are epimers at C-2 form the identical osazones. For the example below, D-glucose and D-mannose, which are C-2 epimers, both produce the same osazone.

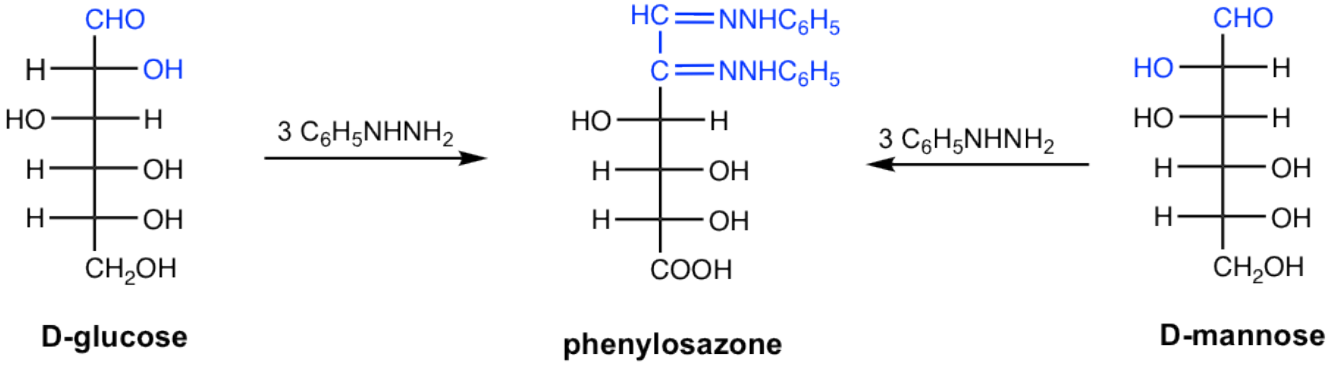


Fig. 9.4l Both D-glucose and D-mannose produce the same osazone when reacting with hydrazine

9.5 Degradation and Synthesis of Monosaccharides

Ruff degradation is the method to shorten the chain of monosaccharides by one carbon atom. It is a process that involves two steps, in which aldose is oxidized by Br_2(aq) to aldonic acid in the first step, and then oxidative decarboxylation occurs by H_2O_2 in the presence of Fe^{3+} to remove one carbon from the structure.

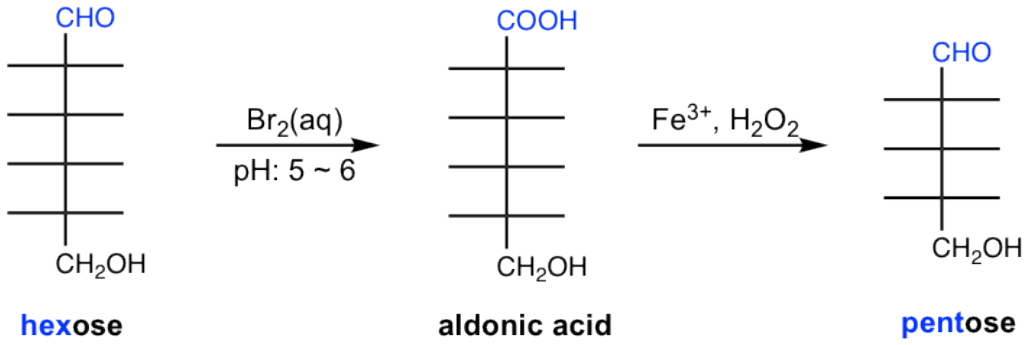


Fig. 9.5a Ruff degradation of hexose to pentose (the OH groups on the middle carbons are skipped)

In the following example, D-galactose is degraded to D-lyxose by the Ruff procedure, and the configurations of all the other carbons remain the same.

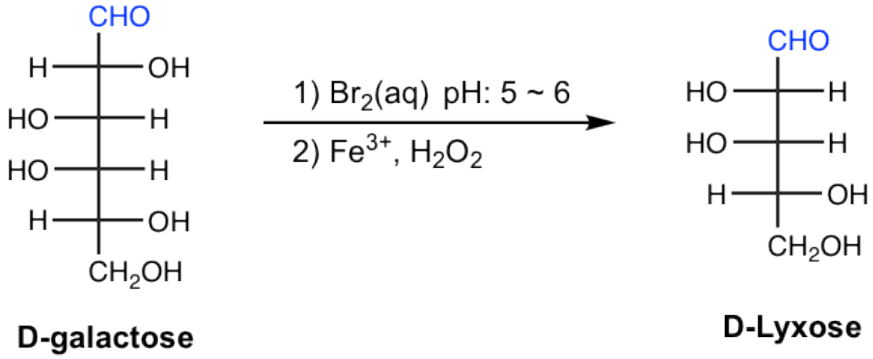


Fig. 9.5b Ruff degradation of D-galactose

9.5.2 Kiliani-Fischer Synthesis

An aldose can be converted to epimeric aldonic acids having one additional carbon through the addition of HCN and subsequent hydrolysis of the cyanohydrins. The aldonic acids stay as lactones preferably, which is then reduced by Na-Hg at pH 3 ~ 5 to aldoses. This method for lengthening the carbon chain of an aldose is called the Kiliani-Fisher synthesis.

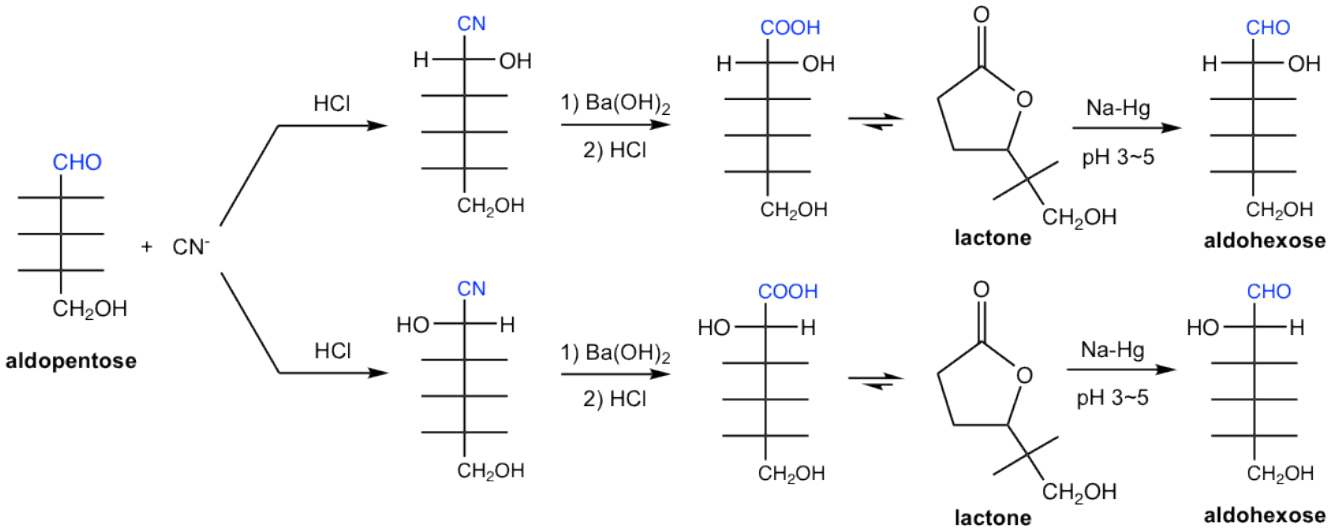


Fig. 9.5c Kiliani-Fischer synthesis of aldohexose from aldopentose (the OH groups on the middle carbons are skipped)

9.6 Disaccharide

Disaccharides are compounds that consist of two monosaccharide units that are connected by a glycoside linkage. Upon hydrolysis, disaccharide gives two monosaccharides.

9.6.1 Maltose

Let's first take maltose as an example. Maltose is a disaccharide that could be obtained from the hydrolysis of starch, and is about 30% as sweet as sucrose (in next section 9.6.2). Maltose contains two D-glucose subunits that are connected by a glucosidic linkage between C-1 of one subunit and C-4 of the other unit, and the oxygen bonded to the anomeric carbon (C-1) is in the α-position. Such linkage can be named as α-(1→4)-glucosidic linkage. The structure is shown in Fig. 9.6a in both Haworth projection and chair conformation.

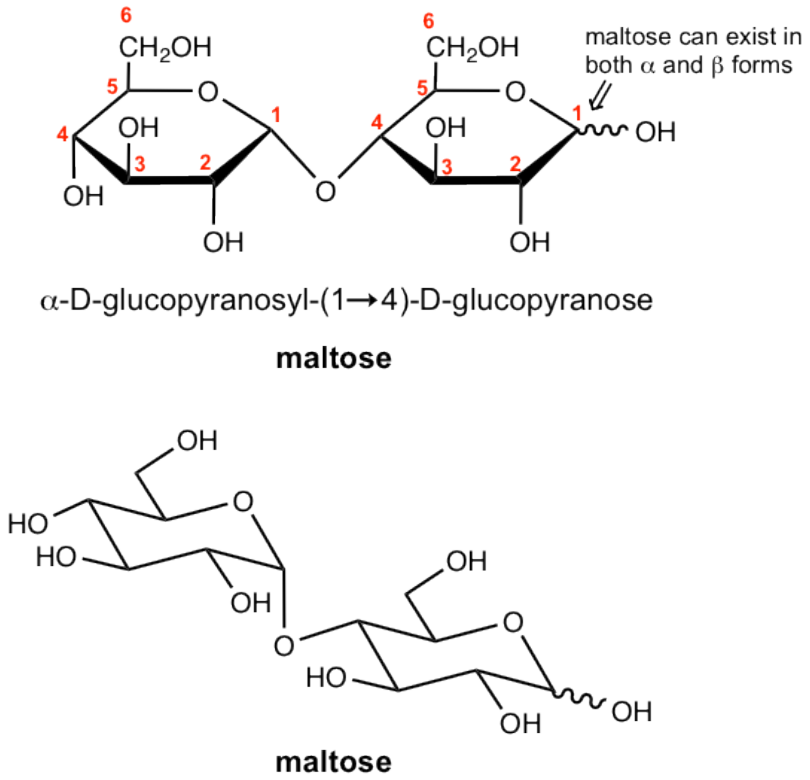
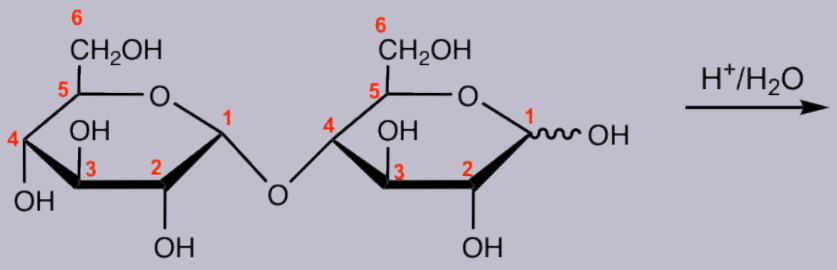


Fig. 9.6a Structure of maltose in Haworth projection and chair conformation

Maltose can exist in both α and β anomers, so the configuration of the anomeric carbon (the carbon with the hemiacetal group) on the right-hand ring is not specified and is marked with a wavy line. Also because maltose has the hemiacetal group in the right-hand subunit, and the hemiacetal is in equilibrium with the open-chain aldehyde and is easily oxidized, therefore it is a reducing sugar that gives positive tests with Benedict's and Tollens' reagents.

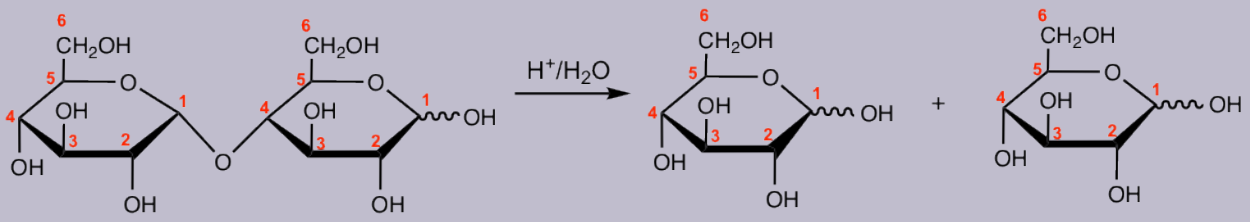
Examples

Show the hydrolysis product of maltose.



maltose

Answer: When 1 mole of maltose undergoes acid-hydrolyzed hydrolysis, it yields 2 mole of D-glucopyranose.



maltose 2 moles of **D-glucopyranose**

9.6.2 Sucrose

Sucrose is the most common disaccharide. It is the substance known as table sugar and is commercially obtained from sugarcane and sugar beets.

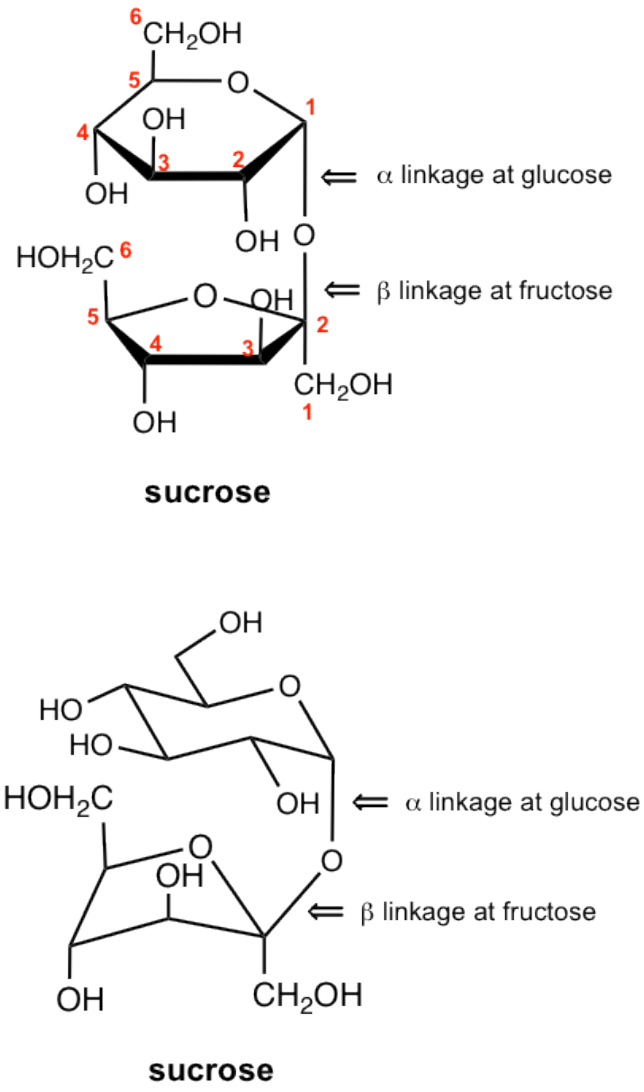


Fig. 9.6b Structure of sucrose in Haworth projection and chair conformation

Sucrose consists of a D-glucose subunit and a D-fructose subunit connected by a glucosidic linkage between C-1 of glucose (in the α position) and C-2 of fructose (in the β position). It is unique among the common disaccharides in the way that the anomeric carbons of both glucose and fructose are tied up. Because the glucosidic bond of sucrose is between the anomeric carbon of both subunits, the molecule does not have a hemiacetal group, so it is not in equilibrium with open-chain form in an aqueous solution, and cannot be oxidized. Therefore, sucrose is a non-reducing sugar.

The hydrolysis of 1 mol of sucrose yields 1 mol of D-glucose and 1 mol of D-fructose. The hydrolysis can be catalyzed by either acid or certain enzymes. The fact that sucrose is only hydrolyzed by an α-glucosidase, an enzyme obtained from yeast, indicates the α configuration at the glucoside portion. The β configuration at the fructoside portion is also confirmed by the experimental result that sucrose is hydrolyzed by sucrase, an enzyme known to hydrolyze β-fructofuranosides.

9.6.3 Lactose

Lactose is a disaccharide found in milk. Lactose consists of a D-galactose subunit and a D-glucose subunit connected by a glycosidic linkage between C-1 of galactose (in the β position) and C-4 of glucose.

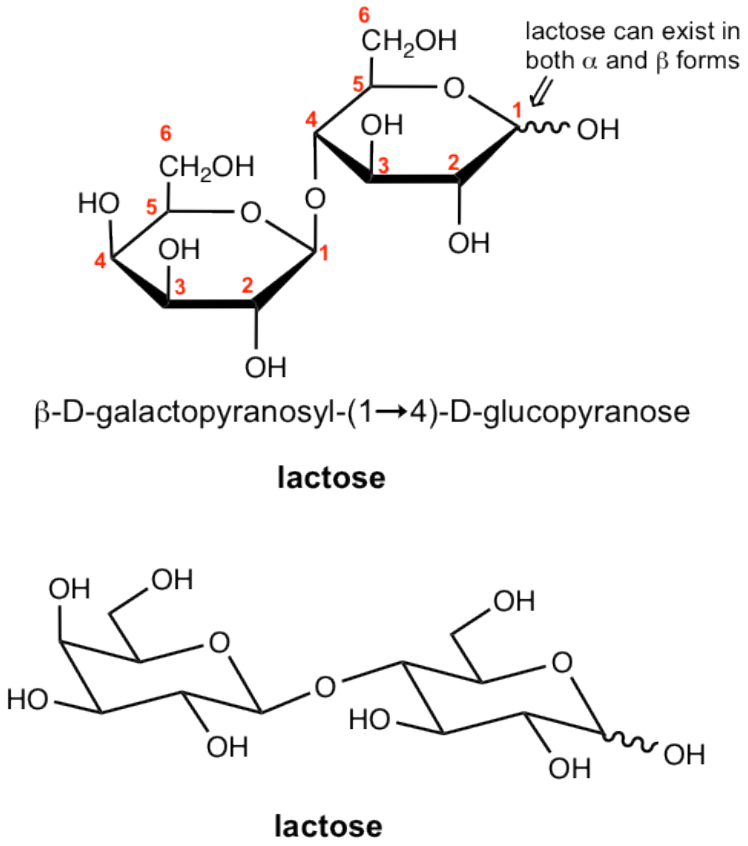


Fig. 9.6c Structure of lactose in Haworth projection and chair conformation

Lactose can also exist in both α and β anomers, similar to maltose, so the configuration of the anomeric carbon (with hemiacetal group) on the right-hand ring is not specified and marked with a wavy line. Also because there is a hemiacetal group in the glucose subunit of lactose, it is a reducing sugar.

9.7 Practices

1. Answer the following questions:

a. Refer to the structures of D-sugars in Fig. 9.1e, and draw the structure of **L-mannose.**

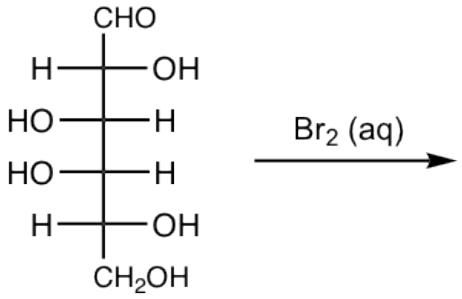
b. D-Mannose is epimer to D-Glucose on which carbon?

c. Draw the β-pyranose form of D-Mannose in both Haworth projection and chair conformation.

d. When D-Mannose is oxidized by nitric acid, an aldaric acid product is obtained. Show the reaction equation with open-chain structures, and determine whether the aldaric acid product is optical active.

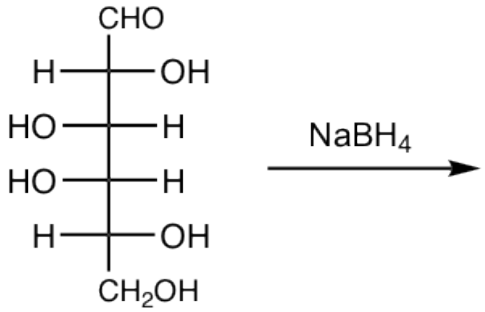
2. Show the product.

a.



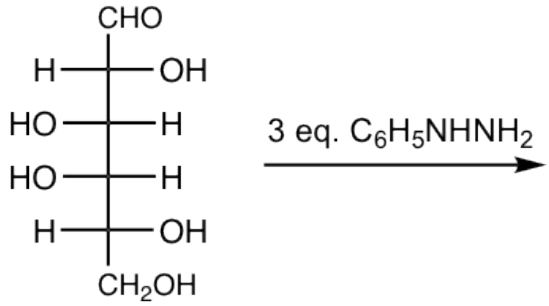
D-galactose

b.



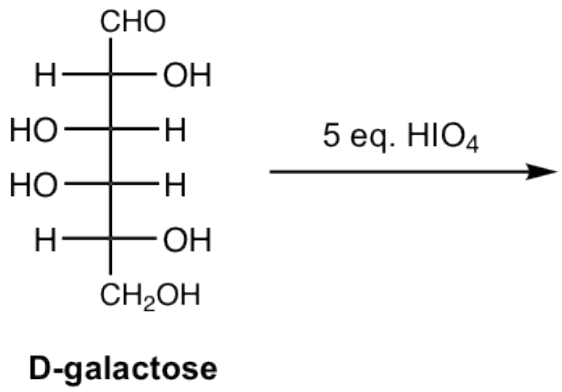
D-galactose

c.



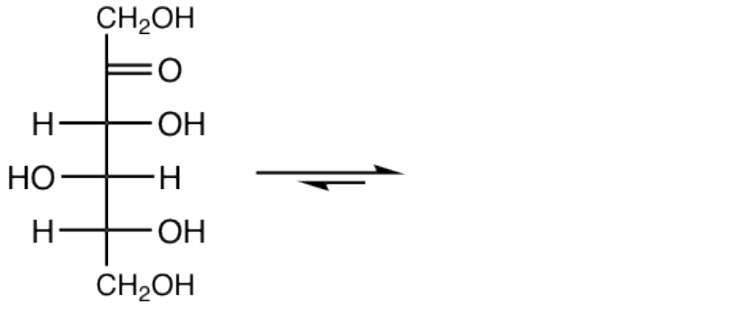
D-galactose

d.



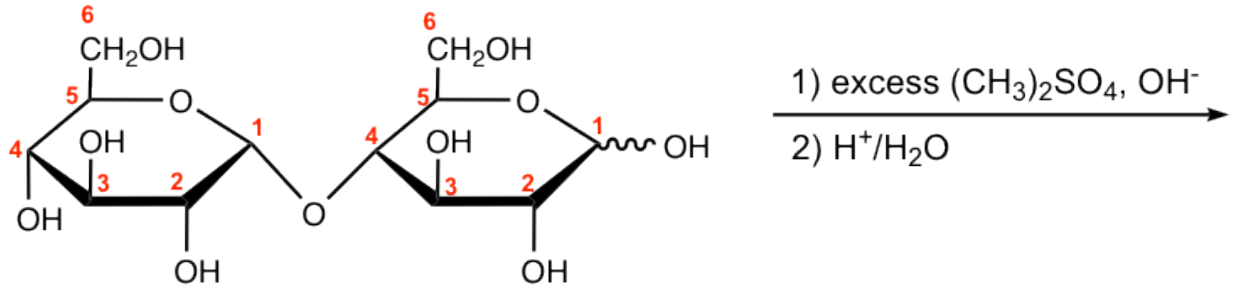
D-galactose

e.



D-sorbose **β-D-sorbofuranose**

f.

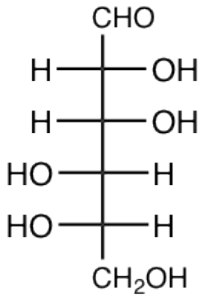


maltose

9.8 Practices Answers

1. Answer the following questions:

a. Refer to the structures of D-sugars in Fig. 9.1e, and draw the structure of **L-mannose.**

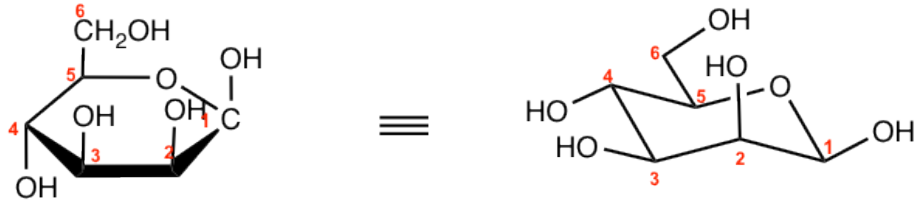


L-Mannose

b. D-Mannose is epimer to D-Glucose on which carbon?

#2 carbon

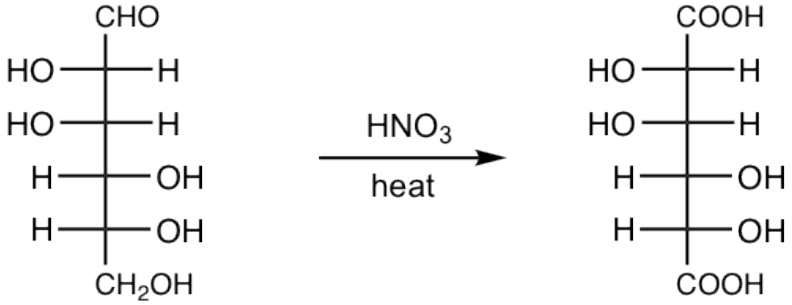
c. Draw the β-pyranose form of D-Mannose in both Haworth projection and chair conformation.



β-D-mannose
Haworth projection

β-D-mannose
chair conformation

d. When D-Mannose is oxidized by nitric acid, an aldaric acid product is obtained. Show the reaction equation with open-chain structures, and determine whether the aldaric acid product is optical active.

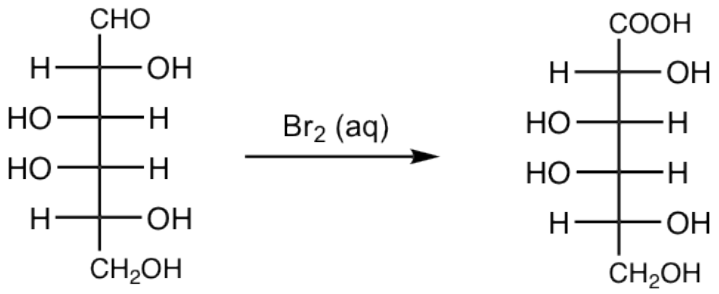


D-Mannose

chiral
optical active

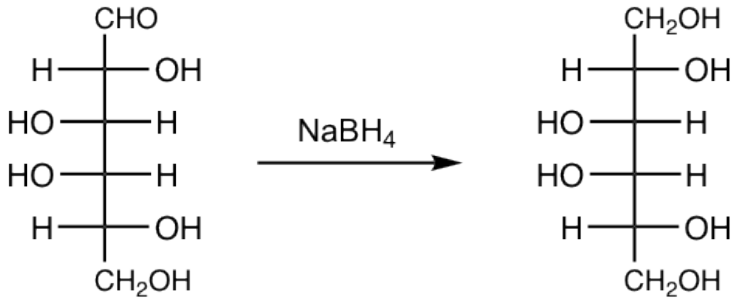
2. Show the product.

a.



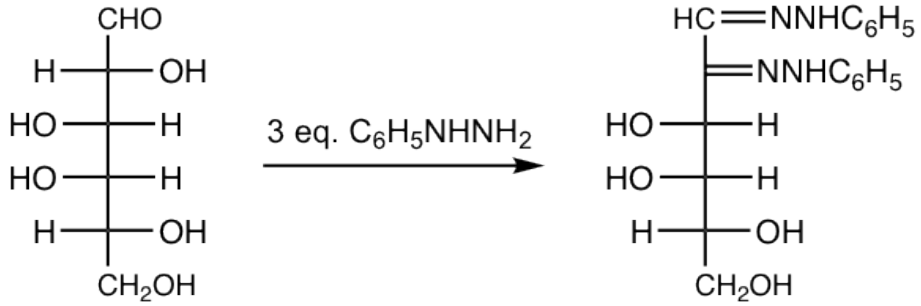
D-galactose

b.



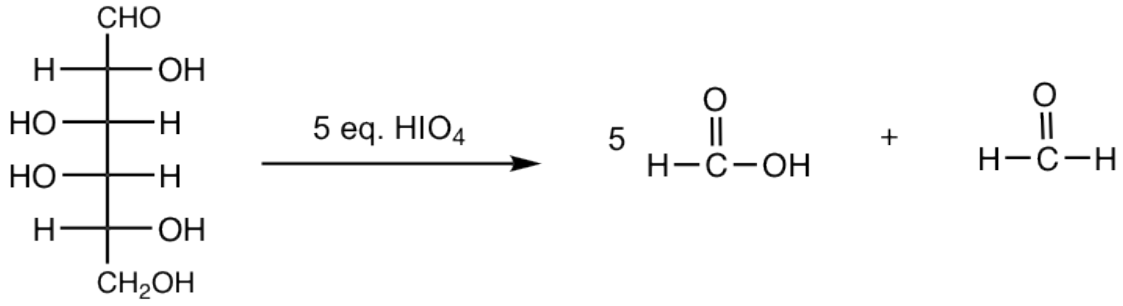
D-galactose

c.



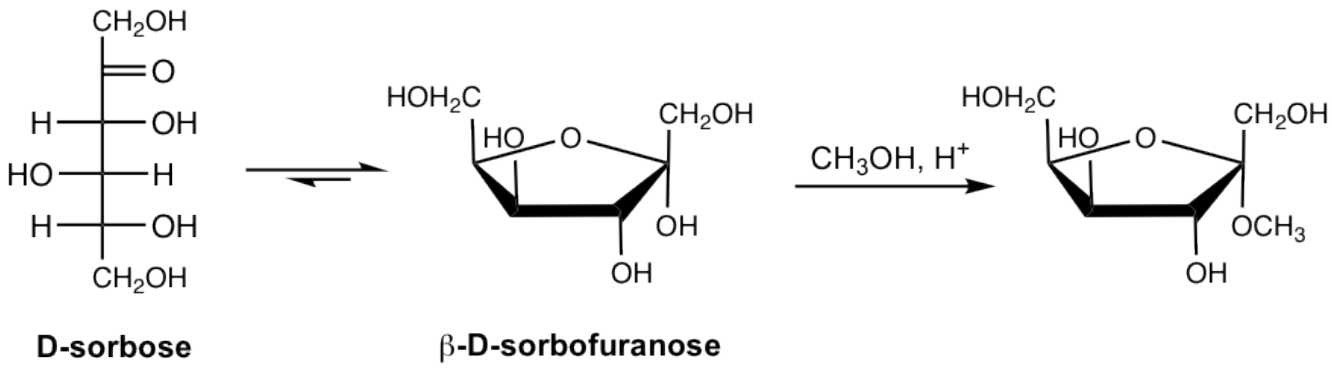
D-galactose

d.



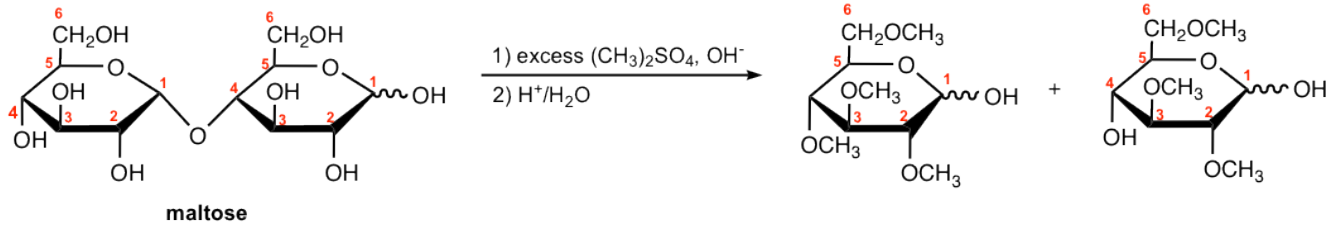
D-galactose

e.



D-sorbose **β-D-sorbofuranose**

f.



maltose

In Organic Chemistry, we always encounter a variety of reaction mechanisms with different names, for example, nucleophilic substitution, electrophilic addition, electrophilic substitution, etc. While it is straightforward to understand "substitution" or "addition", it might be rather challenging, or even confusing, to distinguish between "nucleophilic" or "electrophilic'. A reaction usually involves both nucleophile and electrophile, but why sometimes the mechanism is called "nucleophilic", and sometimes is called "electrophilic"? The purpose of this special section is to help you understand the name of the reaction mechanism clearly and correctly.

We will use the "nucleophilic substitution" mechanism as an example, the mechanism that you are probably most familiar with, to explain the mechanism name.

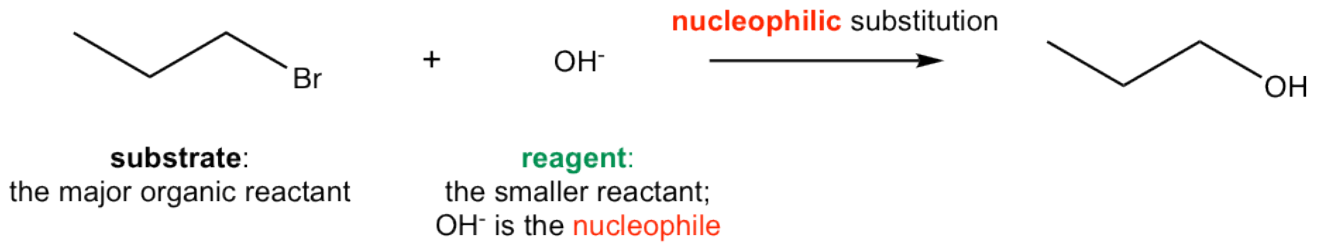


Fig. 10a Mechanism name explanation — Nucleophilic substitution

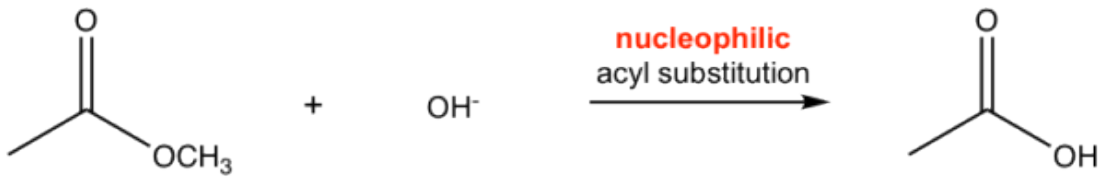
For an organic reaction, the major organic reactant could be called the "substrate", and the other reactants, which are usually smaller, and could be either organic or inorganic, are called the "reagent(s)". The functional group of the substrate is converted to a different one in an organic reaction, for example, the bromide is converted to alcohol in the above reaction.

Whether the name of the reaction mechanism is "nucleophilic" or "electrophilic" depends on the nature of the reagent! That means, if the reagent is a nucleophile, the reaction mechanism is called "nucleophilic", if the reagent is an electrophile, the reaction mechanism is called "electrophilic". For the above reaction, since the reagent hydroxide, OH^-, is the nucleophile, the reaction mechanism is therefore called the "nucleophilic substitution".

That is it! It is not difficult if you know what to look at.

The other common substitution and addition reaction mechanisms we learned in both Book I and this book are summarized below, with an example given for each type of mechanism, for your comparison.

Nucleophilic acyl substitution



substrate

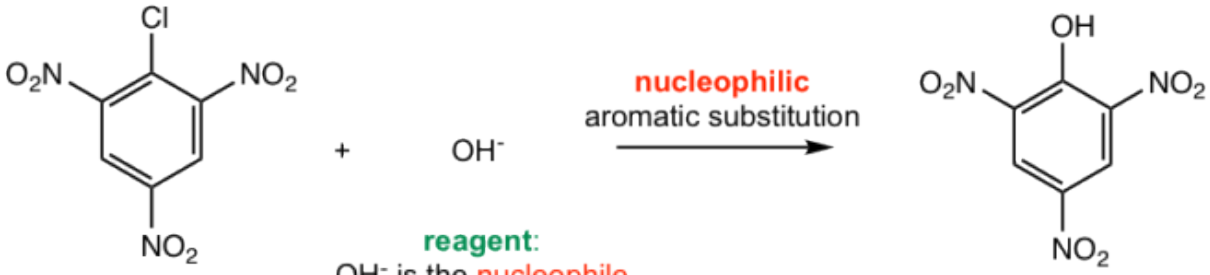
reagent:
OH^- is the nucleophile

Electrophilic aromatic substitution

substrate

reagent:
NO_2^+ is the electrophile

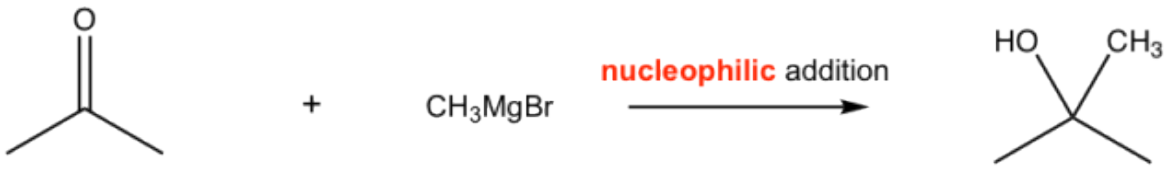
Electrophilic aromatic substitution



substrate

reagent:
OH^- is the nucleophile

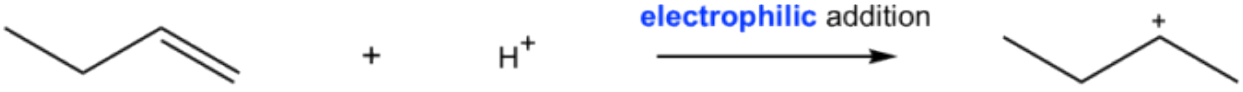
Nucleophilic addition



substrate

reagent:
CH_3^- in the Grignard reagent
is the nucleophile

Electrophilic addition



substrate

reagent:
H^+ is the electrophile

Fig. 10b Summary of reaction mechanisms

Versioning History

This page lists major changes to this book with major changes marked with a 1.0 increase in the version number and minor changes marked with a 0.1 increase.

Version	Date	Change
1.0	20 August 2024	Pressbook Created